

RESEARCH ARTICLE

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# Individual and Integrated Effects of Potential Risk Factors for Oral Squamous Cell Carcinoma: A Hospital-Based Case-Control Study in Jazan, Saudi Arabia

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## Abstract

**Background:** Oral cancer is the sixth most common cancer in the world, with a high prevalence reported in Jazan province of Saudi Arabia. The objectives of this study were to check individual and integrated effects of potential risk factors for oral squamous cell carcinoma. **Materials and methods:** A case control study was designed with a sample of 210 subjects, in which histopathologically confirmed incident cases (n=70) and controls (n=140) matched for age, gender and referral route, were recruited. Differences in exposure to potential risk factors between cases and controls were assessed using chi-square and McNemar analyses. A logistic regression model with interactions was applied to check individual and integrated effects. **Results:** Mean age of the sample was 55 years (+ 20 years). Shammah (O.R = 33.01; C.I = 3.22 – 39.88), shisha (O.R = 3.96; C.I = 0.24 – 63.38), and cigarette (O.R = 1.58; C.I = 0.13, 2.50) consumption was significantly associated (P<0.05) with oral squamous cell carcinoma development. In contrast, Khat chewing (O.R = 0.67; C.I = 0.19-2.36) was without significant effect. An increase in odds ratios was observed when combinations of shammah and shisha (O.R = 35.03; C.I = 11.50-65.66), shisha and cigarettes (O.R = 10.52; C.I = 1.03 – 33.90) or shamma and cigarettes (O.R = 10.10; C.I = 0.50 - 20.40) were used. **Conclusion:** Combined exposure to risk-factors has serious implications and policies on oral cancer prevention should be designed with attention to this aspect.

**Keywords:** Shammah- oral squamous cell carcinoma- oral cancer- case control study -Jazan- Saudi Arabia

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## Introduction

Cancers in general are fatal and around 50% of patient's in developing nations have died while receiving treatment because of its invasive nature (Greenberg 2003; Ghojazadeh et al., 2014; Amirnia et al., 2014; Kumar et al., 2014). Oral cancer in particular, is reported to be rising with a predicted incidence rate of 275,000 new cases per annum (Warnakulasuriya, 2009) thus, making it the sixth most common cancer in the world (Rodriguez et al., 2004). The term "oral cancer" is used in describing the malignancy formed in tissues of oral cavity or oropharynx (Oral Cancer Home Page-National Cancer Institute 2014). Among the cancers occurring in oro-pharyngeal region; 90% are histo-pathologically confirmed as Oral Squamous cell carcinomas (OSCC) (Woolgar, 2006). Population based studies demonstrate an alarming rise in the incidence and prevalence of OSCC globally (Rapidis et al., 2009). In addition, reports have also suggested that there is no significant improvement in their five-year survival rate (Neville, 2002).

According to a report published by World health

organization (WHO), at least 2 out of 100,000 people in the Middle Eastern countries have died due to squamous cell carcinoma (SCC) of the oral cavity. This value is calculated and found to be lower than that of India and other Asian countries (Ferlay et al., 2010). The Cancer registry of Saudi Arabia published their last data in 2006, which ranked oral cancer as the 15th most prevalent cancer among males and 11th most common cancer among females (Brown and Warnakulasuriya, 2006). Data also shows that the prevalence in Saudi Arabia is among the higher side when compared to other gulf countries (CRUK 2013). A study published in the year 2006 reported that nearly 30% of the oral cancer cases (Age standardized ratio = 6.2/100,000 for males and 9.82/100,000 for females) in Saudi Arabia were from Jazan province alone (Brown and Warnakulasuriya, 2006).

Researchers in general have substantiated the frequency and duration of potential factors like tobacco and/or alcohol to be majorly associated with oral cancer (Merletti et al., 1989; Ghojazadeh et al., 2012; Ghojazadeh et al., 2014), while some of them have implicated about the involvement of human papilloma virus (HPV) or a diet

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low in fresh fruits and vegetables (Gil, 2009; Petti, 2009; Attar et al., 2010; Bagan and Jimenez, 2010). Recently, some studies have also comprehensively stated that smoking and alcohol together were accountable for 80% of the oral cancer cases in males, 61% cases in females and 74% cases overall (Warnakulasuriya and Scully, 2005; Gillison, 2007; Petersen, 2009). Another study performed on a subset of Asian population revealed that smokeless tobacco (ST) consumed in different forms is more strongly associated with the increased number of oral cancer cases in comparison to other risk factors (Krishna et al., 2013). These risk factors for a disease may vary in different populations due to the diversity in their life style and socializing behavior.

In Saudi Arabia, there are reports that mention about the use of Shammah (a form of ST) on a frequent basis among the population residing in the southern tip of the Arabian peninsula (Quadri et al., 2015). Apart from ST, few studies have also mentioned about the use of other risk factors such as Shisha (water pipe smoking) and cigarettes; more so among the younger age groups residing in Jazan region (Alsanosy, 2014; Mahfouz et al., 2014; Quadri et al., 2014). Although this region is said to be contributing with the maximum number of oral cancer cases in Saudi Arabia (Allard et al., 1999); there is very limited published data to provide substantial evidence. Also, only a few studies have been performed to analyze the existing potential risk factors leading to oral cancer in this region (Quadri et al., 2015). In addition to that, none of the previous studies have demonstrated interaction effect of risk factors on oral squamous cell carcinoma. Focusing on this knowledge gap, the current study is designed to know the individual as well as the integrated effect of potential risk factors on oral squamous cell carcinoma in Jazan region of Saudi Arabia.

## Materials and Methods

### *Ethical statement and study setting*

Permission from the department of Otorhinolaryngology-Head and Neck Surgery at Faculty of Medicine in Jazan University was primarily obtained. This was followed by an approval from the department of oncology at Prince Mohammed Bin Nasser hospital. It is to be noted that King Fahd hospital and Prince Mohammed Bin Nasser Hospital are the two major tertiary care centers in Jazan where all the suspected cases of OSCC are referred for complete screening and diagnosis. In this study, histo-pathologically confirmed incident cases of OSCC were recruited at Prince Mohammed Bin Nasser hospital from January' 2016 until March' 2017. Informed consent was obtained from each subject before his/her medical data was used for the purpose of this research. Importance and benefits of the current study for the community were also explained to the patients.

### *Study design and sample size calculation*

A hospital based case control study was designed to see the association between OSCC and its potential risk factors. In this study, an issue of over-estimation of the effect of independent variables was possible if the hidden

variables among the studied sample were not taken into account. We increased the probability of solving this issue by selecting controls from the same subset of population and also making sure that they had similar underlying demographic characteristics as the cases.

Sample size calculation was based on two previously performed studies with demographically similar environment (Quadri et al., 2015; Nasher et al., 2014). The probability of exposure among controls as derived from these studies was 0.65. So, with an estimation of 90% power of study and minimum odds ratio of 3, alpha risk of 5% and with case to control ratio of 1:2; the minimum sample required for this study was 200.

### *Study subjects and their inclusion / exclusion criteria* *Cases*

Cases were defined as histo-pathologically confirmed patients with squamous cell carcinoma of oral cavity (OSCC) using International Classification of Diseases (ICD), 10th revision. Subjects were included only if they reported to be residing in Jazan. Patients who visited the hospital setting for diagnosis or treatment of oral cancer from regions other than Jazan were excluded. This was done in order to increase the probability of equal and random distribution of the unidentified risk factors among the sample.

### *Controls*

Twice the number of controls matched with age (+ 5 years), gender and location were selected to justify the power of study (Amtha et al., 2014). Controls were defined as subjects free of OSCC and who followed the same referral route as cases, except that they had approached departments other than that of Oral surgery, Otorhinolaryngology-Head and Neck Surgery and Oncology.

### *Explanatory variables*

Demographic data and details on the assessed explanatory variables like Shammah (Smokeless tobacco), shisha (water pipe), khat (*Catha edulis*) and cigarette were obtained (Quadri et al., 2015). Descriptive data on the use of these potential risk factors were taken from the patient records. This was re-confirmed by contacting each subject recruited in the current study through telephone. These explanatory variables were further dichotomized as "ever users" and "never users". Ever users were considered as subjects who frequently consumed these potential risk factors; whereas "never users" were subjects that had never consumed these substances in their life time.

### *Statistical analysis*

Descriptive details of cases and controls was demonstrated using contingency tables and the relation between these variables was calculated using Chi-square test and McNemar analysis considering a p-value of 0.05 or less as significant. This was followed by a demonstration of binary logistic regression model to explain individual effect as well as the articulated effect of independent variables on OSCC. Separate variables were created by combining the subjects using both shammah and shisha;

OR shamma and cigarette; OR shisha and cigarette for assessing the joint effects. Confounders used while performing the regression analysis were Age, gender, area of living (rural or urban) and level of education. All the data entry and statistical analysis were performed using SPSS version 24 (IBM, U.S.A).

## Results

Current case control study comprised of 210 (N) subjects, in which histo-pathologically confirmed incident cases were 70 (n1) and subsequent controls were 140(n0). The distribution of explanatory variables was significantly different between cases and controls. Percentage of use of potential risk factors was more in cases in contrast to controls (Table 1). There was no statistical difference among the age of cases and controls; Cox and Snell's R-square value showed that the age and gender of the sample were able to predict nearly 5.8% of the regression model.

Individual effect of explanatory variables using the logit model (Table 2) revealed that ever use of shammah (O.R = 33.01, 95% C.I – 3.22, 39.88), shisha (O.R = 3.96; 95 % C.I – 0.24, 63.38) and cigarette (O.R = 1.58; 95% C.I = 0.13, 2.50) were strongly associated (P < 0.05) with

Table 1. Demographic Details and Distribution of Use of Potential Risk Factors among Cases and Controls

Variables	Cases (n <sup>1</sup> =70)	Controls (n <sup>0</sup> =140)	P-Value	<sup>5</sup> O.R
<b>Age</b>				
< 29 years	2.8% (2)	2.8% (4)	0.3	
30 – 59 years	68.5% (48)	68.5% (96)		N.A
> 60	28.5% (20)	28.5% (40)		
<b>Gender</b>				
Male	51.4% (36)	51.4% (72)	0.22	
Female	48.5% (34)	48.5% (68)		N.A
<b>*Shamma</b>				
Never users	17.1% (12)	90% (126)	0	
Ever users	82.8% (58)	10% (14)		3.33
<b>*Khat</b>				
Never users	55.7% (39)	93.5% (131)	0.02	
Ever users	44.2% (31)	6.4% (9)		1.01
<b>*Cigarette</b>				
Never users	42.8% (30)	90% (126)	0.01	
Ever users	57.1% (40)	10% (14)		1.1
<b>*Sheesha</b>				
Never users	18.5% (13)	88.5% (124)	0	
Ever users	81.4% (57)	11.4% (16)		2.23
<b>*Shamma and Khat</b>				
Combined users	42.8% (30)	6.4% (9)	0.02	
Individual users	57.1% (40)	93.5% (131)		1.7
<b>*Shamma and Pipe</b>				
Combined users	80% (56)	10% (14)	0.02	1.67
Individual users	20% (14)	90% (126)		

\*Shamma, Khat, Cigarette and Sheesha consumption was significantly different between cases and controls; McNemar analysis<sup>5</sup> for Odds ratio (O.R); N.A, Not Applicable.

Table 2. Individual Effect of the Predictor Variables on OSCC Adjusted for Age, Gender, Area of Residence and Level of Education

*Explanatory variables	B	<sup>5</sup> P-Value	Crude Odds Ratio O.R (CI)	Adjusted Odds Ratio O.R (CI)
Shamma	3.5	0	67.66 (3.48, 88.79)	33.01 (3.22, 39.88)
Khat	-0.39	0	1.75 (0.19, 3.44)	0.67 (0.19, 2.36)
Cigarette	0.53	0	1.66 (0.17, 33.71)	1.58 (0.13, 2.50)
Sheesha	1.38	0	53.16 (0.11, 76.77)	3.96 (0.24, 63.38)

\*Explanatory variables were dichotomized as “Ever users” and “Never users”; <sup>5</sup>Chi-square analysis was performed to see the association; B, Beta coefficient ; O.R, Odds ratio; CI, Confidence Interval

Table 3. Logistic Regression Model Demonstrating Articulated Effect of Various Potential Risk Factors on OSCC

Predictor variables	<sup>5</sup> P-Value	*O.R (95% CI)	R <sup>2</sup>
<b>Model 1</b>			0.4
Shamma	0	33.01 (13.01 – 76.31)	
Sheesha	0.03	3.96 (2.11 – 28.83)	
<b>Model 2 (Integrated)</b>			0.47
Ever Shamma + Ever Sheesha	0	35.03 (11.50 – 65.66)	
Ever Sheesha + Ever Cigarette	0	10.52 (1.03 – 33.90)	
Ever Shamma + Ever Cigarette	0.02	10.10 (0.50 - 20.40)	

<sup>5</sup>Chi square analysis with P<0.05 as significant; \*Model 2 demonstrating the interaction effect with age, gender, area of living and education level as confounders; O.R, Odds ratio; CI, Confidence Interval.

OSCC; whereas, khat chewing (O.R = 0.67; 95% C.I – 0.19, 2.36) was only meagerly associated. Joint effect was seen through the interaction logit model which is displayed in Table 3. Model 1 predicted about 40% of change in the dependent variable by the explanatory variables. Whereas Model 2, that was designed to record the joint effect of risk factors was able to explain 47% of change in the dependent variable. Combine use of shammah (smokeless tobacco) and shisha (water pipe) increased the chance of OSCC by nearly 35 times (O.R = 35.03; 95 %, C.I = 11.50 – 65.66) in this subset. While, cigarette if used along with shammah (O.R = 10.10; 95% C.I = 0.50 - 20.40) or shisha (O.R = 10.52; 95%, C.I = 1.03 – 33.90) increased the chance of OSCC by nearly 10 times (Table 3).

## Discussion

Increasing rate of oral cancer cases in developing nations is a matter of grave concern for public health practitioners (Ferlay et al., 2010). A thirty-fold difference in age-standardized-rate in Saudi Arabia revealed the existence of demographic disparities among the use of potential risk factors for OSCC (Brown and Warnakulasuriya, 2006). Only a handful of studies have been performed in Jazan even after an indication that the incidence of OSCC is highest in comparison to other regions of the country (Brown and Warnakulasuriya, 2006). The Substance Abuse Research Center (SARC) at Jazan University had also substantiated on the lack of available literature (Alsanosy, 2014). To our knowledge, this study is the first of its kind to explain the joint effect

of shammah, shisha and cigarette on oral squamous cell carcinoma in Jazan region.

Primarily, this study shows that the incidence of OSCC in the year 2016 and 2017 was similar among males and females. A contrasting result was seen in a study performed earlier (Quadri et al., 2015); where oral cancer cases were reported to be slightly more in females than in males. Two other epidemiological studies along with the Globocan report also showed increased prevalence of oral and lip cancer among females residing in Saudi Arabia in comparison to males (Brown and Warnakulasuriya, 2006; Sawair et al., 2007; WHO, 2017). As oral cancer is a complex disease with multiple predicting variables, the investigators here sieved the explanatory variables after reviewing the available research in similar populations across the middle eastern region, thus justifying the exclusion of Human Papilloma Virus (HPV) from the analysis (Brown and Warnakulasuriya, 2006; Alsanosy, 2014; Quadri et al., 2015).

Among the included independent variables in the current study; shammah was seen to be the most important predictable variable for oral squamous cell carcinoma. In accordance with this, previous studies from both developed and developing nations have verified ST in general to be extensively associated with OSCC (Albar, 1994; Jemal et al., 2010; Jemal et al., 2011; Willis et al., 2012; Foulkes, 2013). In addition to that, yet another study by Petersen et al., in a larger population had also substantiated ST to be one of the major causes of oral cancer (Petersen, 2009). In Jazan, smokeless tobacco is popularly known as shammah, which is available in powdered form mixed with carbonate of lime, ash, black pepper, oils and other flavoring agents (Alsanosy, 2014). Most common sites of shammah dipping according to a population based study were buccal mucosa and labial vestibule (Allard et al., 1999). The use of shammah is reported to be extremely prevalent in Jazan region in comparison to other regions of Saudi Arabia (Alsanosy, 2014). In this sample, the mean age after diagnosis of OSCC was 55 years with a high standard deviation. Considering the high standard deviation one may assume that the use of risk factors such as shamma may have been started at a very early age among the studied subjects. In accordance with this, an earlier study revealed that the consumption of shammah in Jazan is sometimes reported to commence among children aged 10-13 years (Alsanosy, 2014). It is also stated elsewhere, that some parents have a myth or belief that shammah helps in reducing dental pain, and they reported to have applied it on infants as a topical medicine (Alsanosy, 2014). Backed by limited evidence we also argue that the consumption of shammah is many times concealed due to personal or legal reasons. In line with this, some researchers have mentioned that its exact prevalence could be much higher than which has been documented (Hannan et al., 1986; Salem, 1992; Allard et al., 1999; Halboub and Al-Mohaya, 2011).

To our surprise, khat (*Catha edulis*) was not seen to be associated with oral cancer in this study. Previous available literature provided mixed views on association of khat with oral cancer. Studies conducted by Soufi et al., (1991); and Fasanmade et al., (2007) had shown

khat to be positively associated with oral cancer; but study conducted by Quadri et al., (2015); displayed a negative association. A systematic review which was performed few years ago had concluded that “association of khat chewing and potentially malignant and malignant oral disorders remains debatable and may require further investigations” (El-Zaemey and Leo, 2015).

The most important finding of this study is the high risk of OSCC due to the combined use of risk factors, and this has not been reported previously. It is seen that shammah if used along with shisha increased the odds of OSCC by nearly thirty-five times. Elsewhere, a similar designed study reporting on the joint effect of cigarette smoking along with alcohol consumption on oropharyngeal cancer also showed significantly high estimates (Ferreira Antunes et al., 2013). Thus, the findings from current study performed in Jazan are unique and successfully contribute to the evidence that shammah dipping is an important explanatory variable for OSCC in this subset of the population.

With regards to its limitations, the authors put forth that the possibility of bias originating from recall is relevant to any case-control study. Also, as this is a hospital based study its findings may not be representative to general population. However, the chances of representation remain high as the study site is performed in one of the two major tertiary centers located in the region. For future, we suggest that further population based studies with larger representative sample should be conducted. We recommend that the duration and frequency of tobacco use should be documented and analyzed for more detailed results. In addition, the authors also suggest that a longitudinal study if conducted will deliver more comprehensive findings. We also insist that a tobacco cessation program is a priority in this region, and this intervention should consist of both psychological therapy (counselling) as well as pharmacotherapy (nicotine patches and lozenges).

In conclusion, to conclude, it is seen that the combined use of risk factors like shammah, shisha and cigarette have serious implications on the onset of OSCC. It is to be emphasized a combined effort from clinicians, public health agencies and other relevant government authorities is required for the future decisions or policy implications on prevention of oral cancer and substance abuse in this region. This can also be escalated by establishing an oral cancer center or a registry in Jazan region of Saudi Arabia.

#### *List of abbreviations*

Oral squamous cell carcinoma: OSCC; Smokeless tobacco: ST; Squamous cell carcinoma: SCC; World health organization: WHO; Odds ratio: O.R; Confidence interval: C.I

#### *Declarations*

Informed consent: Informed and signed consent from all participants was obtained.

#### *Competing interest*

The authors declare that they have no competing interests.

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There is no funding from any external body to support this study.

### Author's contributions

FAH put forth the concept of this study. MFAQ designed the study. Data collection was done by FAH which was later analyzed by MFAQ. Finally, both the authors contributed equally in drafting the manuscript.

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