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Oral Squamous Cell Carcinoma: A 6-Month Clinico-Histopathologic Audit in a Kenyan Population

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Abstract

Objective: To determine the clinico-histopathologic variations and etiological factors associated with oral squamous cell carcinoma (OSCC). Methods: A descriptive cross-sectional hospital based study was conducted at the University of Nairobi Dental Hospital (UNDH) and Kenyatta National Hospital (KNH) between September 2008 and February 2009. Eighty-two (82) patients presenting with lesions confirmed as OSCC were evaluated for habits identified as risk factors such as tobacco use, alcohol use and betel quid chewing. Demographic features including age and gender as well as clinical parameters such as site of the primary lesion, tumour size and nodal involvement were documented. Incisional biopsies were performed for all patients to confirm the diagnosis and histopathological features noted. Results: The mean age of the patients was 58.49 (range = 14 to 90 years), with a male to female ratio of 1.6:1. Remarkably, 13.4% of the patients were aged 40 years and below. The peak incidence was found to have been in the 6th - 7th decades. Tobacco use was the main associated etiological factor (73.2%) followed by alcohol use (57.3%). Notably, 25.6% of the cases had no identifiable risk factor. The tongue was the most common site (35%) followed by the palate (22%) (p = 0.03). The least commonly affected site was the floor of the mouth (10%). The most common stage at presentation was stage IV (52.4%) and; the poorly differentiated OSCC was the most common histopathologic variant (48.8%) followed by the well differentiated (30.5%) and moderately differentiated OSCC (20.7%). Conclusion: In the present investigation it is evident that OSCC has a male predilection with a peak incidence in the 6th - 7th decades and most commonly manifests in the tongue at stage IV with the poorly differentiated subtype being the most common. Of the cases diagnosed 13.4% were aged 40 years and below.

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Keywords

Oral, Squamous Cell Carcinoma, Clinico-Histopathologic, Aetiological Factors

1. Introduction

Oral squamous cell carcinoma (OSCC) is the most common malignant tumour affecting the oral cavity accounting for about 90% of all malignant oral tumours. The incidence varies markedly by geographic region with two-thirds of the cases being diagnosed in developing countries [1]. In Kenya, the relative frequency of oral cancer remains about 2% - 3% with minimal annual variation as reported by Onyango *et al*. (2004) [2]. Generally, OSCC is more common among males and is a disease of the elderly being rarely seen in patients under the age of 45 years. In East, West and Southern Africa, the peak age is reported to be between the 5^{th} - 6^{th} decades, a decade earlier than that in other parts of the world [2]-[10].

The aetiology of OSCC can be attributed to certain interactions between genetic and lifestyle risk factors. In a minority of cases, particularly among the younger patients, common identifiable risk factors are absent, producing a challenge in research into their aetiology. Established risk factors for the development of OSCC include tobacco use, heavy consumption of alcohol, chewing betel quid (pan) especially in the Indian sub-continent, viral infections and the presence of potentially malignant lesions [11]. In most African populations, comprehensive information regarding the pattern of occurrence of OSCC is scanty.

This audit aimed at documenting the clinico-histopathological characteristics and etiological factors associated with OSCC in a Kenyan population and to compare these findings with those of other studies reported in the literature. The knowledge of these characteristics and risk factors is important for clinicians considering the changing trends that are being seen worldwide with reference to age of presentation, gender preponderance and site of occurrence. The histological grade can be used by clinicians to predict the risk of developing cervical lymph node metastasis [12], recurrence/relapse of OSCC after initial treatment [13] and in deciding whether to use neoadjuvant and/or adjuvant radiotherapy in treatment protocols [14] [15].

2. Patients and Methods

2.1. Study Area and Design

The study was based at the University of Nairobi Dental Hospital (UNDH) and at KNH in the Oral Surgery and Ear Nose and Throat (ENT) clinics. UNDH and KNH are the principal referral centres in Kenya where oral and maxillofacial surgical and histopathology services are offered. Patients seen at these centres are referred from all parts of the country while some come on their own.

This was a descriptive cross-sectional hospital based study of patients with a histopathologically confirmed diagnosis of OSCC presenting at UNDH and KNH between September 2008 and February 2009.

All patients presenting to these two hospitals between September 2008-February 2009 with oral lesions that were histologically confirmed as OSCC and who met the other inclusion criteria were included in the study.

2.2. Sampling

A convenient sampling method was used in which all the patients who presented to these two hospitals within the study period of September 2008-February 2009 and met the inclusion criteria were included. Eighty-two patients (82) were recruited for the study. The inclusion criteria included patients presenting to the two hospitals who consented to participate in the study, those with a positive histological diagnosis of OSCC and patients who had not undergone any definitive management for OSCC.

2.3. Clinical Examination

For those patients included in the study, a thorough history was taken including information regarding habits such as tobacco use (smoking/chewing), alcohol consumption, *miraa* and betel quid chewing habits. For each of these habits, the patient was asked if they had ever indulged in them and if they were current users. Tobacco use

included smoking manufactured cigarettes, hand-rolled tobacco, and use of smokeless tobacco. Information on the average number of cigarettes smoked per day was obtained. Smokers were asked regarding the use of filter tipped and non-filter tipped cigarettes. With regard to filters, patients were divided into 3 groups: smokers of filter cigarettes, smokers of non-filter cigarettes and smokers of both products. Information on alcohol consumption referred to commercial beer, traditional brews, wines and spirits, including *chang'aa* (a local distillate). Patients were asked to estimate the average amount of alcohol consumed in each drinking day and average number of days in a month consumed. All this information was recorded in a specifically designed data collection chart which was modified from the American Joint Committee on Cancer (AJCC) staging form for oral cancer.

All the patients were examined by the principal investigator (PI). The clinical characteristics of the disease including site of primary lesion, clinical presentation and staging of the tumour were recorded in the data collection chart. Imaging modalities were used for diagnostic and staging purposes and to verify the presence of metastasis. These included orthopantomograms, computerized tomography (CT), ultrasonograms (U/S) and chest radiographs. Each lesion was staged using the Tumour size, Nodal involvement and Metastasis (TNM) system that is included in the AJCC staging form. All patients aged 40 years and below were subjected to a Human Immunodeficiency Virus (HIV) test (using the fourth generation Enzyme Linked Immunosorbent Assay).

2.4. Histopathological Specimen Analysis

Incisional biopsies were performed on each lesion. For those lesions that were 4 cm and more in the widest diameter, two biopsies were taken 2 cm apart. The specimens were then transported to the histopathology laboratory in 10% formalin. The tissues were examined to record gross descriptions, weights and measurements. Ascending grades of alcohol (70%, 90% through 100%) were used for dehydration of the tissue and removal of the fixative. Clearing of the alcohol was done using chloroform. Each specimen was then embedded in paraffin wax following which thin sections were cut from the blocks. These were stained with haematoxylin and eosin (H & E) to allow for examination under light microscopy.

Data were analyzed using the SPSS for Windows version 17 (SPSS Inc, Chicago IL) and presented in the form of tables, pie charts and bar graphs. Descriptive statistics, measures of central tendency and dispersion and tests of significance (Pearson's chi square (χ^2) test, Fisher's exact test and Binomial test) were used as appropriate. The significance level was set at 0.05.

3. Results

This study included 82 patients among whom 10 (12.2%) were diagnosed at the UNDH and 72 (87.8%) at the KNH. Of the 82 participants in this study, a large number (38 patients) resided in the Central Province of Kenya. **Table 1** summarizes the distribution of patients according to residence.

Among the 82 patients, 61% were male and 39% were female with a male to female ratio of 1.6:1. The mean age at presentation was 58.49 years (range = 14 - 90 years). Males (mean age = 55.9 ± 17.0 years) were found not to have been significantly younger than females (mean age = 62.4 ± 12.8 years ($p = 0.07$). The peak incidence was seen in the 6^{th} - 7^{th} decades (**Figure 1**).

The most common risk factor was tobacco use which was reported in 73.2% of the patients followed by alcohol use (57.3%). The use of miraa (khat) was reported in 9 patients while 4 patients chewed pan. There was no identifiable etiological factor among 25.6% of the patients studied (**Figure 2**).

All the patients who were aged 40 years and below were tested for infection with the Human Immunodeficiency Virus (HIV) and none of them was found to have been HIV positive. Smoking of cigarettes was the most common form of tobacco use having been reported in 60% of the patients among whom 77.7% smoked non-filter tipped cigarettes. Of these, 35 were male while only one was female. Most of the patients (31) were aged 41 years and above. The median duration of smoking was 32.8 years (IQR = 20 - 40 years) while the median number of cigarettes used per day was 10 sticks. The next most common form of tobacco use was chewing which accounted for 23% of the patients. More females (8 patients) chewed tobacco than males (6 patients). Snuff use was reported in 17% of the patients with an equal distribution between the genders. All the patients who chewed tobacco and used snuff were aged 41 years and above.

Considering the patients who consumed alcohol, 42 patients were males and 5 were females. Among these patients, only 5 were aged 40 years and below. The median duration of consumption was 32.7 years (IQR = 24 - 44 years). Traditional brew was the most common type of alcohol consumed (61.7%). The use of both tobacco and alcohol was reported in 39 out of the 82 patients while 5 patients used tobacco, alcohol and chewed khat.

The tongue was the most common site (35%) of OSCC occurrence followed by the palate (22%) (p = 0.03) while the floor of the mouth was the least common site (10%) (**Figure 3**). However, the floor of the mouth (45.5%) and the tongue (42.2%) were the most common sites among cigarette smokers.

Table 1. Distribution of patients according to geographical region of residence.

Province	Number of patients
Central	38
Eastern	26
Nyanza	5
Western	5
North Eastern	4
Rift Valley	3
Nairobi	1
Coast	0
Total	82

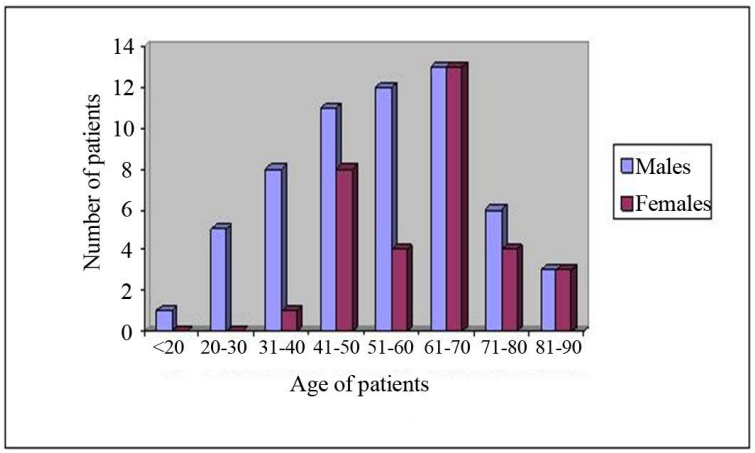


Figure 1. Distribution of patients with OSCC according to age and gender.

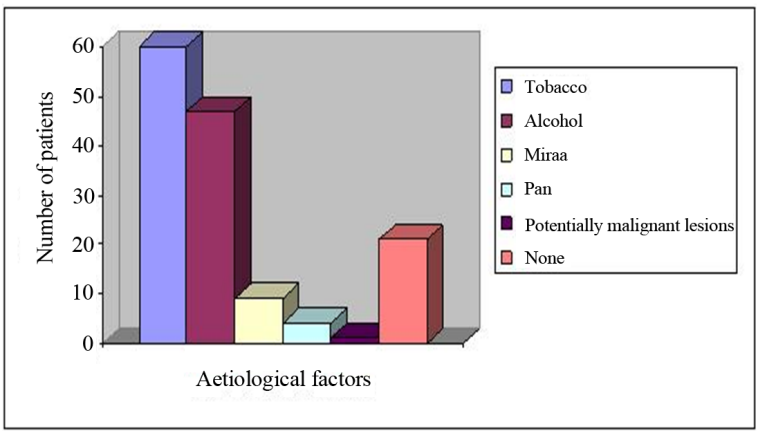


Figure 2. Distribution of patients according to habits associated with the occurence of OSCC.

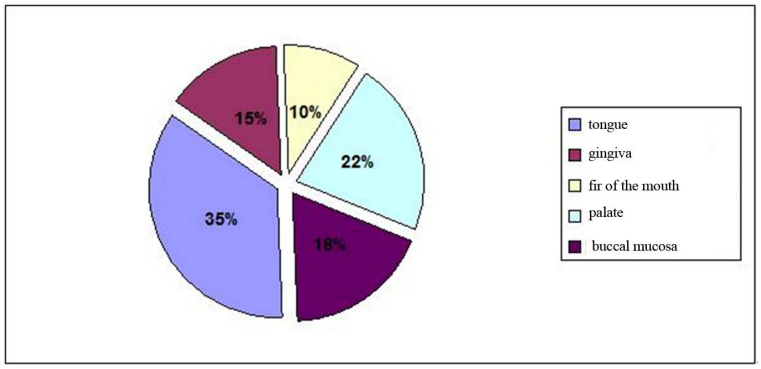


Figure 3. Orofacial site distribution of OSCC lesions.

The most common primary clinical symptoms were ulceration and pain which were reported in 97.6% and 93.9% of the patients respectively. The mean duration of symptoms at presentation was 7.2 months (range = 1 month to 48 months). At the time of diagnosis, most patients were found to have had stage IV disease (53.7%). Stage I disease was diagnosed in 8.5% of the patients while stages II and III accounted for 26.8% and 11% respectively (**Figure 4**).

When assessed further using the TNM system, 41.5% of the patients had T4 lesions at presentation. Most patients (39%) did not have cervical lymph node involvement as assessed clinically and radiologically (with ultrasonography or computer tomography). Only 2 patients were found to have had distant metastasis to the lungs which was confirmed with plain chest radiographs (**Table 2**).

Among the 82 patients, 42 had two biopsies done 2 cm apart whence 36.1% were reported to have had the same degree of differentiation while 61.9% were different. The poorly differentiated OSCC (**Figure 5(a)**) was the most common subtype in both genders (48.8%; M:F = 1.2:1) followed by the well differentiated subtype (30.5%; M:F = 1.3:1) (**Figure 5(b)**) and moderately well differentiated subtype (20.7%; M:F = 4.7:1).

The characteristics of the lesions and their distribution according to gender are summarized in **Table 3**.

4. Discussion

The present study, like other diverse investigations on OSCC executed worldwide, confirms a male preponderance over females with a ratio of 1.6:1 [3] [5] [7]-[11] [16]-[19]. The male to female pattern of affliction has, however, been shown to vary depending on geographical location and anatomical site [20]. Men and women are also almost equally affected in high prevalence regions such as South East Asia [21] [22]. Reversals in the male to female ratios have been reported such as documented by Pathak *et al*. (2009) in Canada where a male to female ratio of 0.9:1 was noted [22]. This study focused on buccal OSCC at a Canadian Cancer centre where the high incidence of the buccal mucosa OSCC among women has been attributed to their use of snuff more than men.

In the present study, the peak age of OSCC occurrence was in the 6^{th} - 7^{th} decades. This differed from other studies executed in Africa where the peak age was found to have been a decade earlier, between the 5^{th} - 6^{th} decades [3]-[8] [10] but tallied with studies conducted in other parts of the world [1]. The peak incidence of OSCC seen in African studies and studies from the Asian subcontinent has been linked to the low life expectancy in these populations and/or early exposure to risk factors [5] [22]. Notably, 13.4% of the cases were patients aged 40 years and below which is similar to other African studies [5] [9] as well as studies done in high prevalence areas such as Thailand (13%) [23], Brazil (12%) [24] and India (7.5%) [21]. This high incidence of young patients with OSCC can be attributed to a higher percentage of young people in the population and the much lower life expectancy as compared with developed countries [5] [22]. Unidentified risk factors among these young patients may also be a contributor to this high incidence.

Tobacco use was the most common risk factor associated with the occurrence of OSCC in the current study further emphasising what has been reported in the literature [1] [17] [25]-[28]. Smoking is the most common form of tobacco use and has been shown to account for an estimated 41% of OSCC cases with the relative risk of developing OSCC in smokers being 6 - 8 times than for non-smokers [29]. Concerning the pattern of tobacco use, more males smoked cigarettes while more females chewed tobacco. This may reflect the culturally accept

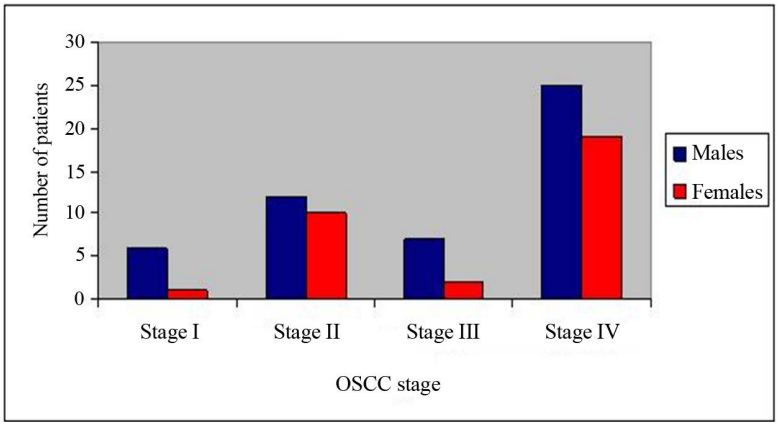
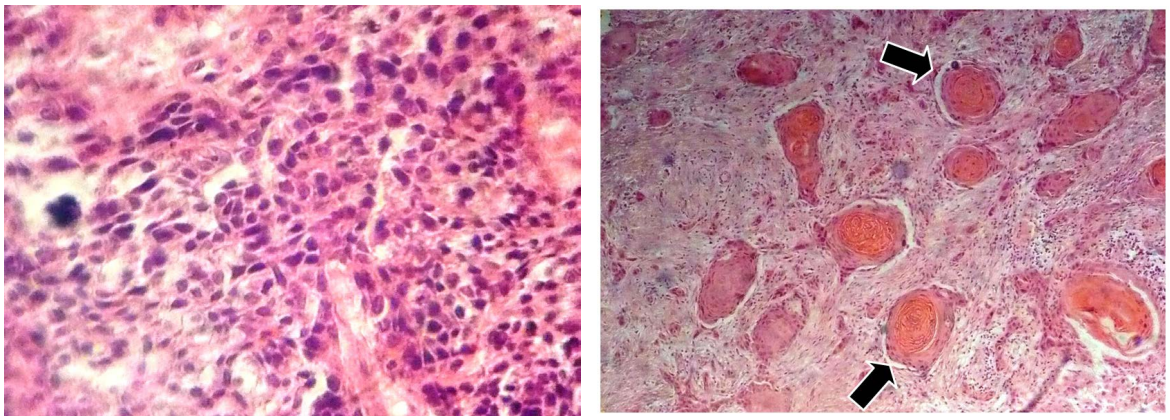


Figure 4. Distribution according to stage of OSCC and gender.

Table 2. Distribution of patients by TNM system.

TNM system		Number of patients
Tumour size (T)	T1	7
	T2	30
	T3	11
	T4	34
Nodal involvement (N)	N0	32
	N1	11
	N2a	3
	N2b	11
	N2c	21
	N3	4
Distant metastasis (M)	M0	80
	M1	2



(a) (b)

Figure 5. Histopathologic variants of OSCC. (a) Poorly differentiated OSCC. Cells have a high mitotic index and the nuclei are hyperchromatic. H & E staining, ×40; (b) Well differentiated OSCC. Several keratin pearls are seen (arrows). H & E staining, ×10.

Table 3. Distribution of histological variants of OSCC according to age and gender.

Age group (years)	Well differentiated		Moderately differentiated		Poorly differentiated		Total N (%)
	M	F	M	F	M	F	
0 - 10	0	0	0	0	0	0	0 (0%)
11 - 20	0	0	1	0	0	0	1 (1.2%)
21 - 30	0	0	3	0	1	0	4 (4.8%)
31 - 40	0	1	2	0	3	0	6 (7.3%)
41 - 50	1	3	1	1	4	3	13 (15.9%)
51 - 60	3	2	3	1	6	1	16 (19.5%)
61 - 70	9	3	1	0	3	10	6 (31.7%)
71 - 80	1	1	1	1	4	2	10 (12.2%)
81 - 90	0	1	2	0	1	2	6 (7.3%)
Total	14	11	14	3	22	18	82 (100%)

able practices among the genders in this population.

Alcohol consumption was the second most common risk factor. Alcohol has been shown not to have direct carcinogenic effects but instead acts synergistically with tobacco to cause a super-multiplicative effect in the oral cavity [30]. It has also been shown that traditional brews which were the most common type of alcohol consumed in this population contain higher levels of congeners such as nitrosamines and other impurities. These act as direct carcinogens in the oral cavity [30]. The risk of developing OSCC also increases with the frequency and duration of alcohol use. The aetiology of OSCC is unknown in a large group of patients as seen in the current study where 25.6% of the patients had no identifiable risk factor. In these patients, OSCC occurrence may be postulated to be due to genetic factors, viral infections among which the most important is the Human Papilloma Virus (HPV) and the diet [21] [27].

Most of the patients in the current series presented with advanced disease with 53.7% of them having had stage IV tumours. This could reflect the delayed treatment seeking behaviour of these patients or delays between presentation of the patients to a primary clinician and referral for treatment. In developed countries most patients present early, therefore, most of them are reported to have stage I and II disease [22] [29].

The site pattern of OSCC was similar to that reported in Kenya by Dimba *et al*. (2007) [9] and Onyango *et al*. (2004) [2] with the most common site affected having been the tongue (35%) followed by the palate (22%). In the former study, the second most common site was the floor of the mouth whereas in the current study this site accounted for the least common site which is in agreement with other studies [2] [4]. This may be attributed to the difficulty in accurately determining the primary site of the lesions especially in patients with advanced disease that extended to the ventral part of the tongue or mandibular gingiva and alveolar ridge. There has been shown to be a correlation between the primary site of the lesion and the risk factor the patient was exposed to. In the current study, the floor of the mouth and the tongue were the most common sites affected in cigarette smokers. The lateral and ventral parts of the tongue as well as the floor of the mouth are particularly sensitive to the local carcinogenic effects of tobacco. This is due to the absence of keratin in these sites and the high concentration of carcinogens in tobacco smoke on inhalation in these areas [30]. The synergistic effect of cigarette smoking and alcohol consumption is more strongly associated with cancer of the floor of the mouth and the posterior tongue because it has been proposed that saliva pools in these gravity-dependent regions concentrating carcinogens there [30].

The poorly differentiated OSCC was the most predominant histological subtype (48.8%) in this study which varies with other studies that have reported the well differentiated type to have been the most predominant [5] [7] [8] [17]. The reason for this difference could be due to the fact that in the current study, two biopsies were performed in 42 patients. The higher grade of differentiation was taken for these specimens, hence the reporting of a higher number of the poorly differentiated subtype of OSCC. The histological grade reflects the aggressiveness of the tumour though it has not been shown to be an independent prognostic factor on multivariate analysis

[12]. The poorly differentiated subtype has been associated with increased risk of developing cervical lymph node metastasis and with recurrence/relapse of OSCC after initial treatment [12] [14]. The presence of a poorly differentiated OSCC is one of the histological risk factors taken into account when deciding whether to use neoadjuvant and/or adjuvant radiotherapy in some treatment protocols [14] [15].

5. Conclusion

In conclusion, the findings of this study confirm that OSCC is the most common among males and the elderly, though remarkably, 13.4% of the patients were aged 40 years and below. The poorly differentiated subtype is the most common histological variant.

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