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# Mapping oral cancer research in South Africa

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## ABSTRACT

The aim of the present study was to review the scope of oral squamous cell carcinoma (OSCC) research in South Africa, including its epidemiology, diagnosis, associated risk factors and management. All publications relating to OSCC on the South African population were sought. A total of 72 studies were included and classified into seven categories; most studies were case reports or case series. Risk factors and epidemiology were the most investigated categories while early detection and diagnosis was the least explored. All the main ethnic groups in South Africa were investigated. The highest incidence of OSCC in South Africa was reported for males of mixed ancestry; there was a male predominance in all ethnic groups except for Asians. There is a high prevalence of OSCC in younger individuals in comparison with the global average. Future research about early detection and diagnosis, risk factors, premalignant lesions, management and disease progression is suggested. Educational programmes are necessary and should include schools and tertiary education institutions to reach adolescents and young adults.

## INTRODUCTION

OSCC ranks amongst the ten most prevalent cancers in the world; being associated with high morbidity and mortality, it constitutes a public health problem.<sup>1,2</sup> As in several low and middle-income countries, lack of access to oral health care can delay diagnosis of OSCC and ultimately decreases survival rates.<sup>3</sup>

It has been recognised that cancers in the oral cavity and oropharynx present wide geographical heterogeneity. In

## ACRONYMS

**HPV:** human papillomavirus  
**NCR:** National Cancer Registry  
**OSCC:** oral squamous cell carcinoma  
**RCT:** randomised controlled trials

South Africa, OSCC derives from a wide geographical area.<sup>4</sup> OSCC in South Africa is the fifth most common cancer in males and the tenth most common cancer in females.<sup>5</sup> Globally, 6% of oral cancers occur before the age of 45; in South Africa, 7.3% of oral cancers occur in males in this age group, and 7.8% in females.<sup>6</sup> Lifestyle-related factors like smoking, alcohol, betel nut and spices consumption, together with other risk factors such as the human papillomavirus (HPV) and persistent inflammation in the oral cavity, are associated with the aetiology of OSCC.<sup>7</sup>

The aim of the present paper is to map archived material of OSCC in South Africa, including research on its epidemiology, aetiology, pathology, diagnosis, associated risk factors and management. Results from this review could help in defining and refining knowledge and voids relating to OSCC research in South Africa.

## METHODS

This report draws on the Arksey and O'Malley methodological framework for scoping reviews.<sup>8</sup>

Inclusion criteria used to identify potential studies:

1. **Anatomical sites:** oral, oropharyngeal, or both.
2. **Fields of study:** premalignant and malignant lesions, leukoplakia, erythroplakia, combined leukoplakia/erythroplakia, proliferative verrucous hyperplasia, carcinoma-in-situ, verrucous carcinoma, and oral squamous cell carcinoma (OSCC).
3. **Study design:** laboratory studies, case reports, case series, case-control studies, cross-sectional studies (including diagnostic accuracy studies), surveys, cohort studies, randomised controlled trials (RCTs) and other clinical trials, screening studies (using Toluidine Blue, chemiluminescence, brush biopsy, and tissue fluorescence imaging) and qualitative studies.
4. **Population:** South African population samples. International multicentre studies where one or more sites in South Africa were included were also eligible.

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Secondary research (e.g. literature reviews) as well as primary studies where the focus was on oral tumours of odontogenic origin, salivary gland origin, tumours of intra-osseous origin, lymphomas, Kaposi's sarcoma and lesions of melanocyte origin were excluded. Studies on lip cancer were also excluded.

**Identification of studies for inclusion**

A Medline electronic search (accessed via PubMed) was performed in October 2012 and updated in January 2014 and 2017, according to the search terms displayed in Table 1. Furthermore, hand searching of reference lists of potentially eligible studies was performed during the screening and data extraction process. The heads of the departments of South African universities in the disciplines of Otolaryngology (eight departments), Oral Medicine and Periodontology (four departments), Oral Pathology (four departments), and Maxillofacial and Oral Surgery (three departments) were contacted via email and asked to send any additional studies that could have been missed by the electronic search.

**Selection of studies and extraction of data**

Two authors independently reviewed the titles from the electronic search results and selected potentially eligible studies. Disagreements were resolved by discussion until

a consensus was reached. The articles sent by the heads of departments were screened for their eligibility.

The following data were extracted from the included articles: category (case reports & case series, prevalence & incidence, risk factors, early detection and diagnosis; premalignant lesions; treatment; and progression of disease); study period; study design, sample size, demographics (gender, age, ethnicity), aim/objectives and main findings. Missing data were described as 'not reported'.

**RESULTS**

The search results and selection process are displayed in Figure 1. In summary, four-hundred-and-two articles were identified through the Medline search, of which 70 were identified as potentially eligible during the screening process. The 19 emails sent out to heads of departments resulted in 46 articles received, of which 22 were included as potentially eligible. Scrutiny of the full texts resulted in 72 studies that met the eligibility criteria. The included studies were classified into seven categories, as displayed in Table 2. Early detection and diagnosis, premalignant lesions and disease progression were the least investigated categories. The earliest included study included was performed in 1964 and the latest was performed in 2014. All the extracted data were summarised in Tables 3 to 10.

Table 1: Medline search strategy	
#1	"Mouth Neoplasms"[Mesh]
#2	"Tongue Neoplasms"[Mesh]
#3	"Oropharyngeal Neoplasms"[Mesh]
#4	oropharyngeal dysplasia
#5	oropharyngeal cancer
#6	oropharyngeal carcinoma
#7	oral carcinoma
#8	mouth carcinoma
#9	tongue carcinoma
#10	oral dysplasia
#11	mouth dysplasia
#12	tongue dysplasia
#13	oral premalignant lesion
#14	oral malignant lesion
#15	mouth malignant lesion
#16	mouth premalignant lesion
#17	oral cancer
#18	mouth cancer
#19	tongue cancer
#20	oral precancer
#21	mouth precancer
#22	tongue precancer
#23	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 #11 #12 #13 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#24	"South Africa" or "Western Cape" or "Northern Cape" or "Eastern Cape" or "Southern Cape" or "Kwazulu Natal" or Limpopo or Mpumalanga or "Northern Province" or "Free State" or Gauteng or Johannesburg or Pretoria or Bloemfontein or "Port Elizabeth" or "Cape Town" or Durban or Umtata
25	#23 and #24

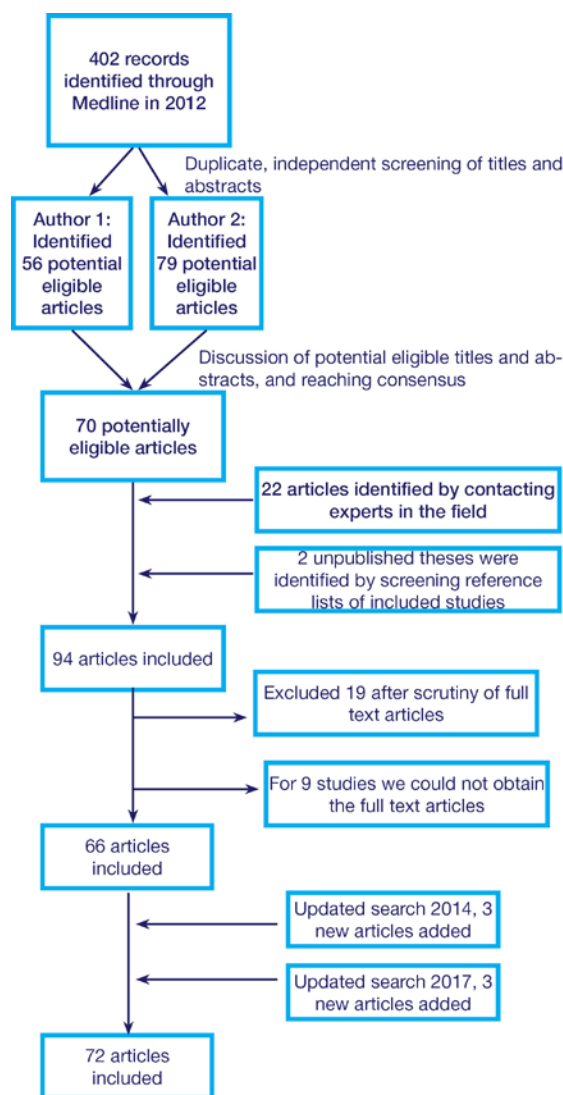


Figure 1: Flow diagram displaying the search results and selection process.

**Table 2:** Categories of OSCC research

Category	Number of studies
Case reports and case series	12
Incidence and prevalence	12
Risk factor	21
Early detection and diagnosis	3
Premalignant lesions	7
Treatment	10
Disease progression	7

Only one of the included studies was a randomised controlled trial (RCT). Due to the higher prevalence of OSCC among older people, most studies included

adults and elderly. All main ethnic groups in South Africa (Whites, Blacks, Asians and people with Mixed ancestry, also referred to as “Coloured”, according to the Population Registration Act n.30 of 1950, repealed in 1991<sup>80</sup>) have been investigated in relation to OSCC, which is important due to the potential influence of ethnicity on OSCC.

Several of the included studies lacked clear objectives; amongst those that explicitly stated the objectives, in many instances the design of the study was not ideal to address the objective. For the studies on risk factors for example, most were case series or cross-sectional, which offer limited information on the topic. Similarly, for the treatment category, only one out of the nine included studies was a RCT, which is the most suited design to evaluate the efficacy of an intervention.<sup>67</sup>

**Table 3:** Studies in the category case reports and case series

First author & year	Study period	Study design	Sample size	Demographics			Aims/objectives	Findings
				Gender	Age*	Ethnicity		
De Waal 2008 <sup>9</sup>	NR	Case series	2	M	adults	NR	To describe a case of OSCC of anterior mouth floor and dorsolateral tongue surface	The dentist should always be aware of changes in the oral mucosa, especially in high risk areas of the mouth in patients that smoke and/or consume alcohol.
De Waal 2008 <sup>10</sup>	NR	Case series	2	NR	adults, elderly	NR	To describe two cases of oral leukoplakia	Identification and control of leukoplakia is necessary in order to decrease the risk of malignant transformation.
Dreyer 2010 <sup>11</sup>	NR	Case report	1	M	elderly	NR	To describe a case of carcinoma of the gingiva and erosive lichen planus	This case emphasises the importance of thorough examination of the oral cavity in all patients. For any deviation from the normal, a biopsy should be performed immediately.
Stander 2013 <sup>12</sup>	NR	Case report	1	M	adult	NR	To describe a case of OSCC of the tongue	This case was not typical; although it was associated with smoking and alcohol use, the patient was younger than the average OSCC patient.
Padayachee 2012 <sup>13</sup>	2009-2011	Case report	1	F	adult	NR	To describe a case proliferative verrucous leukoplakia	This case had a single area with a white benign lesion, which transformed into verrucous carcinoma in the absence of traditional risk factors. Clinicians must be aware of white lesions in older adults.
Padayachee 2010 <sup>14</sup>	NR	Case report	1	F	adults	NR	To describe a case of OSCC of the gingiva related to teeth 31 and 41	This unusual case was associated with HIV and mimicked a periodontal lesion that could have been mistaken by a periodontal abscess.
Mulwafu 2006 <sup>15</sup>	NR	Case series	2	F	adults	Coloureds, Blacks	To describe 2 cases OSCC in patients with discoid lupus erythematosus (DLE).	DLE may have a role in the development of OSCC.
Nortjie 2005 <sup>16</sup>	NR	Case report	1	M	adults	NR	To describe OSCC of anterior mouth floor - Radiological presentation of spread into mandible	Carcinomas in the mandible may result in paraesthesia, pathological fracture, bone erosion and eventual metastasis to regional lymph nodes.
Peck 2010 <sup>17</sup>	NR	Case series	2	F	adults	NR	To describe two cases of OSCC on the dorso-lateral surface of tongue	OSCC have a variety of clinical presentations, and is not always associated with traditional risk factors of smoking and alcohol consumption. One patient was under 45 years.
Peck 2012 <sup>18</sup>	NR	Case report	1	M	adults	NR	To describe a case of oral submucous fibrosis (OSF) and lichenoid interface mucositis	The rare dual lesion could be associated to areca nut or spices used by the patient. The tissue reaction could have been aggravated by the epithelial atrophy in OSF.
Feller 2006 <sup>19</sup>	NR	Case report	1	M	adults	Asians**	To describe a case of leukoplakia	A rare case of proliferative verrucous leukoplakia is presented.
Mamabolo 2006 <sup>20</sup>	NR	Case report	1	M	adults	NR	To describe a case of OSCC of the anterior mouth floor	Taking biopsy on chronic ulcers is critical to provide proper treatment, which is guided by the clinical stage of the disease.

\*Age refers to either elderly (>65 years old), (adult (18 to 65 years old), adolescent (12 to 18 years old), or child (<12 years old)

\*\*Asians include people from Indian descent • M = male; F = female; NR = not reported

Table 4: Studies in the category prevalence and incidence

First author & year	Study period	Study design	Sample size	Demographics			Aims/objectives	Findings
				Gender	Age*	Ethnicity		
Abram 2012 <sup>21</sup>	1997-2001	Data from National Cancer Registry	5470	M+F	All	Whites, Coloured, Black, Asian	To investigate the epidemiology of OSCC in South Africa from 1997-2001	Prevalence of OSCC in subjects <45 years was higher in South Africa (7.3% for males and 7.8% for females), as compared to the global prevalence of 6%. The lifetime risk for developing OSCC and OPSCC is highest for coloured males and lowest for black females.
Hille 1996 <sup>22</sup>	1988-1991	Data from National Cancer Registry	5396	M+F	All	Whites, Coloured, Black, Asian	To present age standardized incidence rates of oral cancer in South Africa	From 1988-1991, 3.4% of all cancer cases in South Africa were oral cancer. The incidence of oral cancer in coloured men was the highest (13.13 per 100.000) of ethnic groups. Major educational programmes are needed.
Ndui 2011 <sup>6</sup>	1996-2002	Data from National Cancer Registry	9702	M+F	All	Whites, Coloured, Black, Asian	To present the epidemiology of OSCC in South Africa from 1996-2002	The total number of OSCC over the 7-year period was 9702, the majority of on the tongue. The male to female ratio was 1:3. The incidence rates was highest for coloured males
Breytenbach 1980 <sup>23</sup>	NR	Cross Sectional	265	M+F	All	Coloured, Indian, Cape Malay	To determine the incidence of oral cancer among the Cape Coloured, Cape Malay, Cape Indian population	The pattern of oral cancer in Cape Coloureds resembles other ethnic groups in South Africa.
Dreyer 1977 <sup>24</sup>	1974-1976	Cross Sectional	722	M+F	All	Cape Malay	To determine the prevalence of leukoplakia among the Malay population of the Cape	Leukoplakia was present in 7.2% of the population and smoking played a major role in most white lesions.
Schonland 1968 <sup>25</sup>	1964-1966	Cross Sectional	3174	M+F	adolescents, adults, elderly	Black	To determine cancer incidence in the Natal African	In the rural areas, incidence decreases with the degree of isolation from the urban areas. Results suggests that the differences found were not correlated to medical care.
Schonland 1968 <sup>26</sup>	1964-1968	Cross Sectional	NR	M+F	adolescents, adults, elderly	Blacks, Indian	To describe OSCC in the Natal African and Indian	Cancer incidence in South Africans from Durban (both sexes) is as high as for most western countries. Indian males have a low overall cancer incidence.
Schonland 1968 <sup>27</sup>	NR	Cross Sectional	99	M+F	adolescents, adults, elderly	Black	To investigate the incidence of oropharyngeal cancers	Several cases of OSCC were included and the prevalence differed in the population groups.
Walker 1999 <sup>28</sup>	NR	Cross Sectional	NR	M+F	All	Asians**	To learn of the current pattern of cancer in the descendants of people who emigrated from India to Durban, South Africa	The main finding was the lower percentage of oral and oropharyngeal cancers in South African Indians in both sexes, as compared to Indian subjects.
Ayo-Yusuf 2013 <sup>29</sup>	1992-2001	Data from National Cancer Registry	16844	M+F	All	Whites, Blacks, Asians, Coloureds	To examine the trends and ethnic disparities in oral and oro-pharyngeal cancers in South Africa during the period 1992 – 2001	Oro-pharyngeal cancers had higher incidence rates for coloured South Africans and lower among Blacks.
Altini 1985 <sup>30</sup>	1971-1980	Case Series	358	M+F	adults, elderly	Black	Age-specific and age-standardized incidence rates for intraoral squamous cell carcinoma in Blacks on the Witwatersrand, South Africa	The age-standardised incidence rates of OSCC are relatively high for South African Black males and low for South African Black females when compared to other countries.
Shear 1970 <sup>31</sup>	1965-1968	Cross Sectional		M+F	adults, elderly	Whites, Black	To investigate the distribution of oral cancer in Africans and Whites in Johannesburg	Oral cancer was more prevalent among males. More African males under 40 years had oral cancer than White males

\*Age refers to either elderly (&gt;65 years old), (adult (18 to 65 years old), adolescent (12 to 18 years old), or child (&lt;12 years old)

\*\*Asians include people from Indian descent • M = male; F = female; NR = not reported

**Table 5:** Studies in the category risk factors

First author & year	Study period	Study design	Sample size	Demographics			Aims/objectives	Findings
				Gender	Age*	Ethnicity		
Chandran 2005 <sup>32</sup>	NR	Case Control	134	M+F	adults, elderly	Whites, Coloured, Black, Asian	To determine the risk of intraoral cancer associated with tobacco and alcohol	Patients who use tobacco and alcohol had ten times more risk to develop oral cancer, as compared non-smokers and non-alcohol consumers.
Darling 1993 <sup>33</sup>	NR	Cross Sectional	579	M+F	adults,	Whites, Coloured	To determine the effects of cannabis smoking on oral soft tissues	Cannabis users presented higher incidence of leukoedema, dry mouth and traumatic ulcers.
Van Rensburg 1995 <sup>34</sup>	NR	Case Series	105	M+F	adults, elderly	Black	Detection of Epstein-Barr Virus (EBV) in OSCC in a black African population sample	There was no evidence for a direct role of EBV in the process of malignant transformation of intraoral epithelial cells.
Bissessur 2009 <sup>35</sup>	NR	Cross Sectional	101	M+F	adults	Indian	To determine areca nut chewing habits in Durban	Areca nut/quid chewing still is a common habit among Indians from Durban, South Africa, including among younger age groups.
Seedat 1988 <sup>36</sup>	1981-1983	Cross Sectional	2058	M+F	adolescents, adults, elderly	Indian	To determine the prevalence of betel-nut chewing and submucous fibrosis in Durban	Betel-nut chewing is very prevalent among South African Indians (5%) and can result in serious health problems, including permanent trismus and oral cancer.
Van Wyk 1993 <sup>37</sup>	1983-1989	Case Series	143	M+F	adolescents, adults, elderly	Indian	To investigate the association of areca nut chewing and OSCC in South African Indians	Areca nut use (alone or associated with tobacco) plays a role in the development of OSCC. Eliminating this habit can decrease the risk for OSCC in 89-91%.
Schonland 1969 <sup>38</sup>	NR	Cross Sectional	99	M+F	adults, elderly	Indian	Upper alimentary tract cancer in Natal Indians	Cancers of the mouth and oesophagus are more prevalent in Indian females than males, which can be related to the higher addiction to betel-chewing amongst females.
Van Rensburg 1995 <sup>39</sup>	NR	Case Series	66	M+F	adults, elderly	Black	Detection of Human Papilloma Virus (HPV) DNA with in situ hybridisation in OSCC in a rural black population	HPV is of limited importance in OSC carcinogenesis in the studies population.
Boy 2006 <sup>40</sup>	1998-2003	Case Series	59	M+F	adults, elderly	Whites, Coloured, Black, Asian	To investigate the detection of HPV in the oropharynx using real time polymerase chain reaction	There was no correlation between HPV detection and OSCC.
Fleming 1982 <sup>41</sup>	1965-1979	Cross Sectional	890	M+F	adolescents, adults, elderly	Whites, Blacks	To establish whether there are differences in the distribution of oral carcinoma between Blacks and whites	OSCC was more prevalent in Black subjects under 50 years of age as compared to white subjects.
Hemmer 2006 <sup>42</sup>	NR	Case Series	10	NR	NR	NR	Is there correlation between ploidy by flow cytometry and chromosome 3 aberration in OSCC	Structural rearrangements involving the long arm of chromosome 3 are infrequent in OSCC.
Davidson 2014 <sup>43</sup>		Cross Sectional	125	M	adults	NR	To examine the presence of human papilloma virus in sample of South African men.	None of the patients who presented oral lesions were positive to HPV.
Pacella-Norman 2002 <sup>44</sup>	1995-1999	Cross Sectional	2900	M+F	adults, elderly	Blacks	To provide recent estimates of the relative importance of some of the suspected risk factors for oesophageal, lung, oral, and laryngeal cancers	Tobacco was the leading risk factor for all cancers.
Postma 2003 <sup>45</sup>	1986-1995	Case Series	99	M+F	adults, elderly	Whites, Coloured, Black	To investigate whether the human papillomavirus is a mutual aetiological agent in oral and cervical squamous cell carcinoma	The results support the idea of systemic susceptibility and infection through a common agent, such as HPV, which could contribute to development of SCC.
Van Heerden 2002 <sup>46</sup>	NR	Case Series	53	M+F	NR	NR	To investigate the suitability of paraffin-embedded material to predict the metastatic potential of OSCC	DNA aneuploidy could predict the metastatic potential of OSCC through DNA flow cytometry from paraffin-embedded primary lesions of OSCC.
Van Heerden 1999 <sup>47</sup>	NR	Case Series	32	NR	NR	NR	Immunohistochemical evaluation of Fhit protein expression in OSCC	Expression of Fhit protein was altered in OSCC, which suggests that the inactivation of Fhit can play a role in oral carcinogenesis.
Van Heerden 2001 <sup>48</sup>	NR	Case Series	17	NR	NR	NR	To investigate the role of Fhit in oral carcinogenesis	Around 60% of OSCC have no expression of Fhit protein, which can play a role in the initiation of OSCC.
Van Rensburg 1998 <sup>49</sup>	NR	Case Series	55	NR	adults, elderly	Black	To determine p53 mutation profile in OSCC of a Black African sample	p53 mutations seem to play a role in oral carcinogenesis. The unique distribution of the mutations suggested different responses to etiological agents.
Van Heerden 1995 <sup>50</sup>	NR	Case Series	120	M+F	adults, elderly	Whites, Black	To investigate the prevalence of Epstein-Barr Virus (EBV) in OSCC in young patients	A possible role of EBV virus in the development of OSCC cannot be excluded, although it does not influence age distribution.
Van Rensburg 1996 <sup>51</sup>	NR	Case Series	146	M+F	adults, elderly	Black	To investigate the presence of HPV DNA in OSCC from an African population sample	HPV is not an etiologic factor in the development of OSCC in the studied population.
Van Heerden 1998 <sup>52</sup>	NR	Case Series	110	NR	NR	Blacks	Correlation between p53 gene mutation, p53 protein labelling and Proliferating Cell Nuclear Gene (PCNA) expression in OSCC	Overexpression of p53 protein was not associated with mutations in the p53 gene.

**Table 6:** Studies in the category early detection and diagnosis

First author & year	Study period	Study design	Sample size	Demographics			Aims/objectives	Findings
				Gender	Age*	Ethnicity		
Afrogheh 2012 <sup>53</sup>	NR	Diagnostic Study	60	NR	NR	NR	To evaluate the use of Shandon Papsin liquid-based oral test (PS LBC) using a novel cytological scoring system	The Shandon PS LBC in association with transepithelial brush biopsy technique is a highly sensitive, specific and economical screening test to detect malignancy. The proposed oral cytological grading system correlates well with histology.
Rawamugira 2012 <sup>54</sup>	2007	Randomized Controlled Trial	65	M+F	adults, elderly	Black	To determine the uptake of an oral health screening program	Screening uptake should be improved; the strategy used to improve knowledge and awareness was successful (pamphlets).
Van Heerden 1995 <sup>55</sup>	NR	Case Series	50	NR	NR	NR	To determine the inter-observer reproducibility of the invasive cell grading method on OSCC and to correlate this with the DNA ploidy status and Langerhans cell (LC) population	The method for invasive cell grading is reproducible; however, there was no correlation between the grading results and ploidy status or LC count.

\*Age refers to either elderly (>65 years old), (adult (18 to 65 years old), adolescent (12 to 18 years old), or child (<12 years old)

\*\*Asians include people from Indian descent • M = male; F = female; NR = not reported

**Table 7:** Studies in the category premalignant lesions

First author & year	Study period	Study design	Sample size	Demographics			Aims/objectives	Findings
				Gender	Age*	Ethnicity		
Van Wyk 1977 <sup>56</sup>	NR	Cross Sectional	585	M+F	adults, elderly	Coloureds	To determine the oral health status of institutionalized elderly Cape Coloureds from the Cape Peninsula	White lesions were more prevalent in males and positively associated with tobacco use.
Randeria 1982 <sup>57</sup>	NR	Case Series	18	Female	adolescents, adults	Indian	To describe submucous fibrosis as a premalignant lesion	The epidemiological, clinical and cytological aspects of this study serve as a diagnostic model for early detection of this premalignant lesion.
Chandran 2013 <sup>58</sup>	1990-2010	Retrospective Cohort	95	M+F	adults, elderly	Whites, Black, Asian, Coloured	To analyse differences in clinicopathological features of oral leukoplakia in different racial groups in the greater Johannesburg area of South Africa	Black South Africans had more non-homogenous leukoplakia (23%) than whites (13%); dysplastic oral leukoplakia was more prevalent in whites (51%) as compared to black South Africans (23%). The floor of the mouth was the most frequently affected site in whites, in black people it was the buccal mucosa.
Feller 1991 <sup>59</sup>	NR	Case Series	130	M+F	adults, elderly	Whites, Black, Asian	A clinicopathological study of premalignant lesions of the oral mucosa in a South African sample.	Leukoplakia was present predominantly in white males and smokers. The peak age was the 7th decade. The sites most frequently affected were the buccal mucosa and floor of mouth.
Stein 2008 <sup>60</sup>	1995-2004	Cross Sectional	9690	M+F	adults, elderly	Black	To assess the effects of tobacco smoking on cancer and cardiovascular disease in urban black South Africans.	Risk for cancers of oral cavity/pharynx was significantly higher among current than never-smokers. Cigarette consumption is relatively low in this population, but the odds ratio for cancer is similar to those from Western countries.
Shear 1967 <sup>61</sup>	NR	Prospective Cohort	1000	M+F	adults, elderly	Pakistanis	Oral submucous fibrosis in South African Indians: An epidemiological study.	Betel nut chewing may cause submucous fibrosis, a premalignant oral lesion. Programs must target Indians to inform on the potential health hazards of this habit.
Van Zyl 2012 <sup>62</sup>	2000-2008	Case Series	110	NR	NR	NR	To evaluate the use of high-resolution flow cytometry on formalin-fixed, paraffin-embedded tissue of leukoplakia from the tongue and floor of mouth and to correlate the findings with the histologic grading.	The ploidy status of premalignant lesions, as determined by high-resolution flow cytometry, may be of value in predicting biological behaviour and malignant transformation of leukoplakia.

\*Age refers to either elderly (>65 years old), (adult (18 to 65 years old), adolescent (12 to 18 years old), or child (<12 years old)

\*\*Asians include people from Indian descent • M = male; F = female; NR = not reported

**Table 8:** Studies in the category treatment

First author & year	Study period	Study design	Sample size	Demographics			Aims/objectives	Findings
				Gender	Age*	Ethnicity		
Ebrahim 2011 <sup>63</sup>	2002-2009	Case Series	107	NR	NR	NR	To investigate the incidence of metastasis to the submandibular gland in patients with head/neck squamous cell carcinoma	Submandibular gland metastasis from head and neck primary SCC is rare, preservation of the ipsilateral submandibular gland during neck dissection is oncologically safe, except in case of prior surgery or radiotherapy, or primary tumour close to the gland.
Harris 2011 <sup>64</sup>	NR	Prospective Cohort	47	M+F	adults, elderly	NR	Timing of drain removal following head and neck surgery	Drains can be removed safely when volume falls to <50 ml over 24-h period. This would result in less morbidity, shorter hospital stays and cost savings.
Hudson 1994 <sup>65</sup>	1983-1989	Case Series	15	M+F	adults, elderly	NR	The role of suprahyoid block dissection in treating carcinoma of the floor of the mouth	Combined with radiotherapy, suprahyoid block dissection is effective for treatment of nodal carcinoma of the floor of mouth, presenting low morbidity.
Jones 1992 <sup>66</sup>	1977-1986	Case Series	32	NR	adults, elderly	NR	To investigate the survival times relating to major surgery of oral and oropharyngeal carcinoma	Survival at 3 years was 50%, at 5 years was 25%. Prognosis and complications were adversely influenced by advanced TNM staging.
Mills 1988 <sup>67</sup>	NR	Randomized Controlled Trial	20	M+F	adults	NR	To monitor the dose modifying effect of beta-carotene during an intensive course of radiation and chemotherapy when treating OSCC	Beta-carotene seems to be associated with protection of the mucosal membrane within the radiation fields used.
Mulwafu 2006 <sup>68</sup>	1999-2004	Case Series	15	NR	adults, elderly	NR	To evaluate the suprahyoid approach to treatment of squamous cell carcinoma of the base of the tongue	The suprahyoid approach for OSCC of the base of the tongue provides good exposure, local tumour control and excellent functional outcome.
Van Lierop 2008 <sup>69</sup>	1998-2004	Case Series	8	NR	adults	NR	To determine whether total glossectomy for advanced tongue carcinoma is justified	Total glossectomy and postoperative radiotherapy is a reasonable option for treatment in developing countries, with higher cure than radiotherapy alone.
Van Lierop 2008 <sup>70</sup>	1999-2004	Case Series	14	M+F	adults	NR	To review the use of the buccinator myomucosal flap in treatment of a case of OSCC	The buccinator myomucosal flap is a good option for reconstruction of small and medium defects in the oral cavity and oropharynx, with low risk failure.
Meyer 2012 <sup>71</sup>	2007	Case report	1	F	adults	NR	To describe the use of the buccal fat pad in treatment of a case of OSCC	The pedicled buccal fat pad is reliable for small oral defects and oro-antral fistulae. Radiotherapy can begin after epithelialization is complete.
Engelbrecht 2007 <sup>72</sup>	2004	Qualitative Study	2	M	adults	White	To determine the quality of life of two participants who had undergone total glosso-laryngectomy	Total glosso-laryngectomy has a high impact on quality of life. Achieving oral communication and having a good support structure can help improve quality of life.

\*Age refers to either elderly (>65 years old), (adult (18 to 65 years old), adolescent (12 to 18 years old), or child (<12 years old)

\*\*Asians include people from Indian descent • M = male; F = female; NR = not reported

**Table 9:** Studies in the category disease progression

First author & year	Study period	Study design	Sample size	Demographics			Aims/objectives	Findings
				Gender	Age*	Ethnicity		
Hemmer 1995 <sup>73</sup>	NR	Prospective Cohort	386	NR	NR	NR	Flow cytometric cellular DNA content and lymph-node metastasis in OSCC	DNA flow cytometry can help determine the risk for metastasis from primary OSCC. Metastasis in diploid tumours appear to be delayed by 2 years.
Mckenzie 2009 <sup>74</sup>	2006	Case Report	1	M	adult	Asians	Discussion of axillary nodal metastasis at primary presentation of an oropharyngeal primary carcinoma	Although rare, axillary nodal metastasis can occur with primary oropharyngeal SCC, reason why the axilla should be routinely examined in those patients.
Naidu 2012 <sup>75</sup>	2004-2009	Case Series	69	M+F	adults	NR	To evaluate the incidence of submandibular gland metastases in cases of oral cavity OSCC	There was an absence of metastasis to the submandibular gland in OSCC. Patients with early stage OSCC and stage zero neck may be candidates for preservation of the submandibular gland during neck dissection.
Hemmer 1997 <sup>76</sup>	1986-1995	Prospective Cohort	93	NR	NR	NR	To investigate the presence of DNA ploidy in OSCC	Aneuploid tumour cell lines acquire properties that make them capable of invasion and metastasis. Diploid primary tumours have excellent prognosis with radical surgery.
Hemmer 1996 <sup>77</sup>	NR	Case Series	348	NR	NR	NR	To investigate the relationship between flow cytometric DNA ploidy and recurrence of OSCC	There is an association between the DNA ploidy status of the primary tumour and the risk of metastasis.
Mahomed 2007 <sup>78</sup>	NR	Case Series	30	NR	NR	NR	To determine whether analysis of E-cadherin and/or beta-catenin expression can aid in the identification of OSCCs likely to metastasize	E-cadherin and b-catenin play a key role in tumour progression and loss of differentiation in OSCC, but their use as prognostic markers appears unreliable.
Van Heerden 1999 <sup>79</sup>	NR	Case Series	32	NR	NR	NR	To investigate the expression Fhit protein in OSCC	For mild/moderate epithelial dysplasia, Fhit expression was seen in the superficial layers, while severely dysplastic lesions had absence of Fhit expression. Fhit expression was reduced or absent in 66% of OSCC.

\*Age refers to either elderly (>65 years old), (adult (18 to 65 years old), adolescent (12 to 18 years old), or child (<12 years old)

\*\*Asians include people from Indian descent • M = male; F = female; NR = not reported



## DISCUSSION

### Case reports/case series

The several case reports and case series highlighted the importance of the biopsy for abnormal lesions in the oral cavity in order to avoid delays in the diagnosis of OSCC. Most cases were associated with tobacco use and alcohol consumption; however, a few cases of OSCC were reported in younger patients in the absence of traditional risk factors.<sup>12,17</sup> Reports on oral cancer in HIV-infected and discoid lupus erythematosus patients suggest a possible role for these conditions in relation to OSCC.<sup>14,15</sup> With the alarming statistics for HIV in South Africa, 12.7% of the population is HIV-positive (Government Statistical Release 2016<sup>81</sup>); the development of non-AIDS related cancers requires further attention.<sup>82</sup>

### Prevalence and incidence

In South Africa, the National Cancer Registry (NCR) compiles pathology-based data on cancer in the country. The most recent studies on prevalence and incidence of oral cancer in South Africa relies on data extracted from the NCR database. Globally, oral cavity and oropharynx cancers combined account for approximately 5% of all cancers in males and 2% of all cancers in females; the number of new cases per year for both genders is estimated at 310.000.<sup>83</sup> In South Africa, from 1997-2001, 5% of all cancers in males and 0.6% of all cancers in females were oral cancers; 0.6% and 0.1% were cancers in the oropharynx of males and females, respectively.<sup>6,21,22</sup>

The average age standardized incidence rate (ASIR) for oral cancer in South Africa from 1996-2001 was 6.2/100.000/year for men and 1.6/100.000/year for women.<sup>5</sup> The combined ASIR for both genders was 4.5/100.000/year<sup>29</sup>, which is not far from the global average ASIR of 5.1/100.000/year from the Globocan database.<sup>1</sup>

Differences among ethnic groups were observed, with Coloured males having the highest ASIR for oral cancer (10.2/100.000/year), followed by white males (6.9/100.000/year). Asian women had the highest ASIR amongst females (3.4/100.000/year), followed by Coloured and White women (both 2.8/100.000/year). The only ethnic group where females had higher ASIR than males was the Asian group. In subjects under 45 years of age, there was no male prevalence.<sup>6,21</sup>

The majority of oral cancers were diagnosed at the end of the sixth decade; the population average age at time of diagnosis was 57.8 years.<sup>29</sup> In South Africa, the incidence of cancers in the oral cavity and oropharynx in males (7.3%) and females (7.8%) younger than 45 years is higher than the global average (6%).<sup>6</sup> Rural populations seem to present lower incidence of OSCC as compared with urban groups.<sup>26</sup>

Oral cancer in Sub-Saharan Africa presents estimated mortality rate of 2.8/100.000/year for males and of 1.0/100.000/year for females for cancer of the lip and oral cavity combined.<sup>4</sup> A global estimate from the US for the 5-year relative survival rates for oral cancer is based on the clinical stage at diagnosis, with 82% for localized lesions, 52% for regional lymph node involvement and 27% for

patients with metastasis.<sup>84</sup> It must be pointed out that, since only cancers diagnosed histologically are included in the NCR, the real burden of oral cancer in South Africa can be worse than hitherto reported.<sup>21</sup>

### Risk factors

Traditional risk factors such smoking and alcohol consumption play a crucial role in the aetiology and pathogenesis of OSCC worldwide.<sup>7</sup> Globally, oral cancer is more prevalent in males and so is smoking; in South Africa the gap among genders is large, while 32% of adult men smoke, only 8% of adult women are smokers (WHO report 2015).<sup>85</sup>

The use of potentially carcinogenic leaf products such as areca nut, associated or not with tobacco, adds to the complexity of aetiological factors for oral cancer in South Africa.<sup>4</sup> The habit of chewing areca nut can maybe explain the higher prevalence of oral cancer in female South Africans of Indian heritage as compared to male Indian South Africans.<sup>26,35,37</sup> It has been reported that up to 93% of adult South African Indian women chew areca nut/quid.<sup>37</sup>

The potential role of infection with HPV16 and 18 infection in OSCC has been investigated worldwide, especially in non-smoker younger patients.<sup>86,87</sup> Neither HPV nor Epstein-Barr virus were associated with OSCC in South African subjects.<sup>34,40,51</sup> One case series investigated alterations in chromosome 3 in relation to OSCC and suggested that mutations in the short arm of chromosome 3 may play a role in the progression of OSCC.<sup>42</sup>

Globally, low socio economic status has been associated with increased odds ratio for development of oral cancer (OR up to 2.4), measured as low income, educational level and social class.<sup>88</sup> Furthermore, a pooled analysis of 16 studies showed that each portion of fruit or vegetables consumed per day decreases the risk for oral cancer (OR 0.5).<sup>89</sup> In a country with much inequity such as South Africa, it is surprising that no study has evaluated the role of low socio economic status and dietary deficiency for oral cancer.

### Early detection and diagnosis, premalignant lesions and disease progression

Despite advances in research and surgical techniques, the 5-year survival rate for OSCC remains low, with a rough estimate of 50%.<sup>1</sup> The high morbidity and mortality rates emphasize the importance of screening programmes and techniques for early detection of malignancy. Although exfoliative cytology has been investigated as a pre-screening alternative,<sup>53</sup> the gold standard for diagnosis of cancer of the oral cavity and oropharynx remains the biopsy.<sup>90</sup> Visual examination is still the best screening tool; guidelines from the American Dental Association suggest that cytology can be useful for patients with suspicious lesions that refuse to undergo biopsy.<sup>91,92</sup>

Leukoplakia is the most common premalignant lesion, the overall risk for malignant transformation in oral leukoplakia lesions is estimated at 2%. The majority of leukoplakia (80%) reported in South Africa affects white subjects.<sup>68</sup> Oral submucous fibrosis is another recognized premalignant condition, with an estimated malignancy transformation rate of 3.7%.<sup>93</sup> Chewing of areca nut, a common habit among Indian and Indian-descendant women, is a significant

risk factor for developing oral submucous fibrosis.<sup>57,61</sup> More studies are necessary to better understand the carcinogenesis of those premalignant lesions.

It is estimated that in approximately 40% of patients with OSCC, the disease progresses through metastases in cervical lymph nodes, which worsen prognosis and survival rates.<sup>94</sup> Submandibular and axillary lymph nodes are rarely affected, but should be examined routinely.<sup>74,75</sup> Studies have suggested that DNA flow cytometry can help identify the risk for metastasis in primary OSCC tumours.<sup>73,76,77</sup> Understanding the progression of the disease and its metastatic potential can help improve survival rates.

The search for prognostic markers of disease progression for OSCC in South African subjects has not yet been successful according to studies on the expression of E-cadherin and b-catenin.<sup>78</sup> Fhit protein has been investigated as a potential prognostic factor, since the tumour suppressant FHIT gene seems to be inactivated in severe dysplastic OSCC lesions.<sup>79</sup> Prognosis of tongue cancer has been reported as worse when this protein is under expressed; however the clinical application of this finding is still to be determined.<sup>95</sup>

### Treatment

Surgical techniques for oral cancer treatment have been the primary focus of studies on OSCC management in South African subjects, highlighting that most lesions are diagnosed at a late stage.<sup>3</sup> Surgery is the main treatment strategy for oral cancer patients worldwide, especially in advanced stages. A study from 1992 reported a 50% survival rate at 3 years and 25% at 5 years for South Africans submitted to major surgery for OSCC.<sup>66</sup>

Radiotherapy is usually used as an adjunctive treatment after surgery for advanced lesions. Chemotherapy has not been commonly used for oral cancer treatment, however, there has been a trend for its use combined with surgery and radiation in advanced or recurrent cases.<sup>96</sup> The use of molecular targeted drugs holds promise on less debilitating treatment options for OSCC patients worldwide.<sup>97</sup>

### CONCLUSIONS

OSCC is a significant problem in South Africa, resulting in morbidity and mortality. Ethnic and gender variations are present, with males of mixed ancestry, having the highest incidence rate of OSCC in the country. Smoking and alcohol consumption are strong risk factors for OSCC in the general population. The prevalence of OSCC in young subjects (<45 years) in South Africa is higher than the global average and not always associated with traditional risk factors.

Generally, there is a paucity of information on premalignant lesions, early diagnosis, traditional and non-traditional risk factors, disease progression and management of cancers of the oral cavity and oropharynx in South Africa. Although there seems to be enough information on the epidemiology of OSCC in the country, an underestimation of the incidence and prevalence cannot be excluded.

Various studies mention the need for educational programmes and public health policies targeting risk

factors and early identification of lesions, which ideally should translate into less invasive treatment, better quality of life and lower mortality rates. Educational programmes should include schools and tertiary education institutions to reach adolescents and young adults.

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