

**A COMPARATIVE ANALYSIS OF CLINICOPATHOLOGICAL
CHARACTERISTICS AND TRENDS OF ORAL SQUAMOUS CELL CARCINOMA
BETWEEN MALES AND FEMALES OVER A TEN YEAR PERIOD**

By

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Declaration

I, Tashta Mohangi, declare that this research report is my own, unaided work. It is being submitted for the degree Master of Science in Dentistry at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Tashta Mohangi

_____ day of _____ 2016 in _____

For my little sister, Tahlia.

“Sail forbidden seas. Land on barbarous coasts.”

Abstract

Introduction: Oral squamous cell carcinoma (OSCC) is a significant disease burden in South Africa. The literature shows that OSCC has historically affected males more frequently than females due to the presumption that males indulge in high-risk habits more commonly. However, the incidence of OSCC in females is increasing as a result of changing lifestyle and risk factors. The aim of this study was to compare the clinicopathological characteristics and trends of OSCC between males and females, diagnosed at the Department of Oral Pathology, University of the Witwatersrand over the ten-year period 2004 to 2013.

Methods: This study was a retrospective, descriptive and comparative study. A total of 1049 records of OSCC cases diagnosed between 2004 and 2013 were reviewed; clinicopathological data were recorded and statistically analysed.

Results: There was a decreasing trend in the number of diagnosed OSCC since 2004 (167 cases in 2004 to 87 cases in 2013). However, there was an increase in female cases of OSCC (22.1% in 2004 to 37.9% in 2013). The number of female smokers increased by 11% since 2004. The mean age at which cases presented was 57.3 years (range of 2 to 93 years). Males presented at a younger mean age of 56.7 years (range of 18 to 93 years) than females at 58.7 years with a range of 2 to 92 years. The lateral surface of the tongue (20.1%) was the most commonly affected site, and OSCC of the upper lip was more prevalent in females than in males ($p = 0.0004$).

Conclusion: This study highlights the differences in the presentation of OSCC between males and females in the Gauteng province region, and especially raises awareness of OSCC in females. It could lead to male and female all-encompassing diagnostic and management protocols.

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Nomenclature, abbreviations and symbols

OSCC: Oral Squamous Cell Carcinoma

SCC: Squamous Cell Carcinoma

OAP: Oral and Pharyngeal Cancers

HPV: Human Papilloma Virus

EBV: Epstein-Barr Virus

KSHV: Kaposi Sarcoma Herpes Virus

MCP: Merkel Cell Polyoma Virus

HBV: Hepatitis B Virus

HCV: Hepatitis C Virus

HTLV-1: Human T-Cell Lymphotropic Virus Type-1

OPSCC: Oro-Pharyngeal Squamous Cell Carcinoma

HPV-DNA: Human Papilloma Virus Deoxyribonucleic Acid

HAART: Highly Active Anti-Retroviral Therapy

NHL: Non-Hodgkin Lymphoma

HIV/AIDS: Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome

IARC: International Agency for Research on Cancer

XP: Xeroderma Pigmentosum

BCC: Basal Cell Carcinoma

TNM: Tumour Size, Nodal Involvement, Metastasis

PNI: Perineural Involvement

ICD: International Classification of Disease

H&E: Haematoxylin and Eosin

SAS: Statistical Analysis Software

CHAPTER ONE

1.1 Introduction and literature review

Oral cancer is increasingly affecting the South African population. It is a malignancy which is reportedly more prevalent in developing countries and has not received the same amount of attention as other more prevalent cancers of the developing countries, including South Africa; such as lung and prostate cancer in males and breast and cervical cancer in females (1–5). Oral and pharyngeal cancers are a significant disease burden in South Africa (6).

Oral cancer is the sixth most common cancer globally (7). The term “oral cancer” encompasses many different malignant neoplasms that occur in the oral cavity, including: carcinomas, sarcomas, lymphomas and melanomas, with the most common being oral squamous cell carcinoma (OSCC) which makes up 90% of all oral malignancies (4,7–13). There are 275,000 new cases of OSCC diagnosed each year worldwide and the morbidity and mortality of OSCC have not significantly improved during the last thirty years (2,13–16). Although OSCC is usually described as a disease of the elderly, the incidence and prevalence of OSCCs in young people are increasing (14,15). The prevalence of OSCC varies between geographical locations, and within these locations, a further variation exists between genders, racial groups and cultures. These differences are influenced by the level of country development, genetic factors and exposure to different risk factors (10,17,18).

According to the most recent National Cancer Registry of South Africa for 2011, cancers of the mouth encompass 1.04% of all cancers in the country. In the male category, Blacks were reported with the highest percentage of mouth cancers at 1.92% while in females, Asians were the highest at 1.21% (19). The literature shows that OSCC has historically affected males more frequently than females due to the presumption that males indulge in high-risk habits more commonly (10,20–23). Males in India, Brazil, Iraq and South Africa are shown to develop OSCCs twice as often as their female counterparts (10,20–22). This ratio may indicate that males in these countries are exposed to high-risk habits more frequently than their female counterparts.

Some studies have also explored the gender-specific factors implicated in the development of cancers. Dorak et al in 2012 pitted autosomal chromosomes against sex chromosomes and found that gene expression changes were the most common intermediate phenotype between genetic variants and modification of disease risk. They however, also reported that in cancer susceptibility, the role played by the environment is much greater than that of genetics. It was thus postulated that genetic factors are more likely to be modifiers of susceptibility rather than primary determinants of susceptibility. The same authors found that several factors may contribute to the development of gender disparity in general disease susceptibility; including sex hormones, genetic differences, environmental causes, gender-linked differences in the skin, epigenetics, microchimerism, and autophagy. A collective belief is that the male excess in cancer incidence is due to variation in environmental and occupational exposures, including smoking, diet and sunlight exposure. Although environmental exposures were shown to dominate overall cancer risk, environmental variations alone could not explain the sex differential in cancer risk. Differences in environmental exposures for each cancer that is more common in either sex are known for few cancers but not as a general phenomenon. Dorak et al in their report mentioned that any differential exposure would have to apply to young adults and children who have little cumulative exposure to environmental genotoxins. They concluded that if not all, some contribution to male excess in cancer is expected to come from genetic factors (24).

In South Africa, however, a difference exists between the genders in Black and White racial groups. The average male to female ratio of OSCC in Black patients was shown by Khammissa *et al* in 2014 to be almost 4:1 whereas in White patients, it was around 2:1 (10). The variations in OSCC prevalence between different countries, geographic locations, ethnic and racial groups have been attributed to exposure to different environmental factors and ethnic-specific high-risk habits (3). It has been reported that OSCC is more prevalent in developing countries than in developed countries (2–4). Ayo-Yusuf *et al* in 2013 studied the trends and disparities of oral and pharyngeal (OAP) cancers in South Africa over the period 1992 to 2001 (6). The findings of this study were consistent with the literature and highlighted OSCCs of the lip as being a common occurrence among Whites, linked to the high smoking rate and low melanin skin pigmentation (2,6). Ayo-Yusuf *et al* found that South African females, particularly those of Indian ancestry had a high incidence of OSCC that was related to the habit of betel quid chewing. Similarly, it was shown that the use of oral snuff was more common in Black females who also showed an increased incidence of OSCC (6). Ethnic and

racial disparities can also be seen abroad in Ashkenazi Jews who present with OSCC more than Sephardic-Jews of Israel, in Indian migrants living in England more than Indians that were born in England, in African Americans more than in White Americans as well as in South Africa where Black South Africans are affected by OSCC more than White South Africans (3,10,25–27). It has been postulated that factors such as socioeconomic status, level of education, cultural influences and varied access to health care services could be responsible for these ethnic and racial disparities and, thus, significantly influence the morbidity and mortality of patients with OSCCs from disadvantaged backgrounds (3,27).

A 2:1 male to female ratio in South African Whites is in keeping with most other developing countries, whereas, the result of 4:1 in South African Blacks is substantially higher (10). In 2008, 2009, 2011 and 2014 respectively, Norway, Nigeria, Thailand and Mexico showed a more equal male to female distribution of around 1:1 (16,28–30). This ratio aligns with a globally reported trend of decreasing differences of OSCC prevalence between genders (2,16,31). Females are showing a higher incidence of OSCC now than they did in the past, a phenomenon that has been attributed by many authors to changes in social and daily activities such as tobacco smoking and alcohol consumption, unknown environmental factors, an increased recent trend in smoking among females and the increasing incidence of Human Papillomavirus (HPV) -related carcinomas (12,28–30,32–34). It is estimated that viral infections are responsible for up to 15% of cancer cases worldwide and about 20% of cancers in developing countries, such as South Africa (35). More than one hundred different types of HPV have been described and at least fifteen have been classified as high-risk due to their epidemiological association with oropharyngeal and cervical cancers (36,37). HPV subtypes 16 and 18 are most commonly found in malignancies of the cervix, and recently, of the oropharynx and oral cavity (38,39). Low-risk HPV is found in benign lesions like verruca vulgaris and squamous papilloma (40).

Lingen *et al* in 2005 concurred with Chaturvedi *et al*, Gillison *et al*, Herrero *et al* and Dahlgren *et al* when they stated that, “Human papillomavirus infection is the principal cause of a subset of oropharyngeal squamous cell carcinoma (OPSCC). Epidemiological associations with sexual behaviour and HPV exposure are strong and consistent for OPSCC, but less so for OSCC” (41–45). However, Syrjanen *et al* in 2011 found a significant association between pooled HPV-DNA detection and OSCC (OR = 3.98; 95% CI: 2.62–6.02) (46). Like other authors, they also found an association between HPV and oral potentially malignant diseases like, oral leukoplakia, oral condyloma acuminatum and oral lichen planus

(41–43). In contrast, studies by van Rensburg *et al* in 1995 and Boy *et al* in 2006 found HPV to be of limited importance in oral squamous cell carcinogenesis as a minority of OSCC specimens tested positive for HPV in both studies (47,48).

Chaturvedi *et al* in the United States observed an increasing incidence of HPV-related cancer in White males but not in White females, (41) while Patel *et al*, also in the United States found an increasing trend in White females as compared to White males (49). Over the past three decades, the incidence of OSCC has been decreasing, while the incidence of OPSCC has been increasing (50). The overall decline in tobacco use and the association of the carcinogenic strains of HPV with OPSCC may explain this trend.

According to Butt *et al* in 2012, the Human Immunodeficiency Virus (HIV) has caused the biggest change in cancer patterns in Africa, with Kaposi sarcoma now the most common cancer in males and the third most common in females (51). HIV-positive patients now have a longer life expectancy due to the widespread use of highly active antiretroviral therapy (HAART). However, this may lead to the development of diseases that require a long latency period, such as cancer. Among HIV-positive patients, the most common cancers in the head and neck region have previously been Kaposi sarcoma and non-Hodgkin lymphoma (NHL). However, OSCC is now being diagnosed much more frequently in HIV-positive patients (51).

Immunosuppression as a risk factor for the development of OSCC has traditionally been described in organ transplant patients who develop OSCC of the lip secondary to immunosuppressive therapy (52). Globally, but most especially in South Africa, a more rampant immunosuppression exists in the form of HIV/AIDS. Southern and Eastern Africa is currently home to the highest number of people living with HIV/AIDS in the world with 17.1 million adults and children living with HIV, 5.6 million of which live in South Africa (53). Characterized by profound immunosuppression which itself is a risk for malignancy, HIV may have a critical impact on the emergence of OSCC in the South African population (54). The EC Clearinghouse classification of 1993 for oral lesions in HIV infection shows several malignant neoplasms that are associated with HIV; these include KSHV and non-Hodgkin lymphoma (NHL) (55). Both of these neoplasms are commonly seen in the oral cavity of HIV-positive South African patients and have been linked to the loss of immune control for oncogenic viruses; while an elevated risk for the development of non-AIDS-defining cancers exists due to persistent immunosuppression, co-infection with oncogenic viruses and a high prevalence of lifestyle-related cancer risk factors like tobacco smoking and alcohol

consumption (54,56–58). Given the high prevalence of HIV, it therefore could be a cogent assumption that HIV might be a high-risk factor for the development of OSCC among South African patients. Host immunosuppression can greatly increase the likelihood of SCC development, recurrence, and malignant spread (58–62). Immunosuppression may be due to a number of factors, including an underlying malignancy, the active use of immunosuppressive agents during transplant therapy, or infection with HIV (63).

Warnakulasuriya *et al* in 2005 categorised tobacco smoking, tobacco chewing and alcohol consumption as risk factors that are well established for the development of OSCC (64). In Western countries, the two most common risk factors for the development of OSCC are tobacco use and alcohol consumption which, when used together, are strongly synergistic (1,13,64–69). Cigarette smoking has been shown to increase the risk of OSCC by 3 times in females and 1.9 times in males while a daily alcohol intake increases the risk of both genders developing OSCC by up to three times (70). A person would be 35 times more likely to develop OSCC by daily concurrent smoking and drinking than one who does not (16,70,71). Tobacco smoking in any of its various forms was shown to be carcinogenic in humans by the International Agency for Research on Cancer (IARC) in 1986 (72). The use of tobacco products in South Africa is primarily regulated by The Tobacco Products Control Act 83 of 1993. This act governs many aspects of tobacco control, including public smoking restrictions, packaging and labelling of tobacco products and tobacco advertising, promotion and sponsorship. The most common form of tobacco use in Western countries is cigarette smoking while the chewing of tobacco is most common in Asian countries where the high incidence of OSCC is attributed mostly to the chewing of betel quid, which is a combination of betel leaf, areca nut and slaked lime (16,20,71,73–75). However, due to the large number of immigrants as well as people who adopt Asian customs for recreational purposes, the use of betel quid and chewing tobacco outside of Asia is not uncommon. The chewing of tobacco together with betel quid increases the exposure of the chewer to carcinogenic tobacco-specific nitrosamines (TSNA) and to nitrosamines derived from areca nut alkaloids. Reactive oxygen species (ROS) have been implicated in carcinogenesis and are generated in substantial amounts in the oral cavity during tobacco chewing. Tobacco smoke pro-carcinogens, such as benzo-[a]-pyrene, are metabolised by oxidising enzymes, particularly cytochrome p450, resulting in the production of reactive carcinogenic intermediates. Alcohol may act as a solvent and enhance the penetration of carcinogens into target tissues. Acetaldehyde, which is an alcohol metabolite, has been identified as a tumour promoter (1).

The use of snuff is an acceptable and common practice among Black females in South Africa and Africa at large. Snuff is a smokeless tobacco which in its use is usually placed in the muco-buccal fold. In Africa, Kabwama *et al* in Uganda found 2.9 % of their cohort to be daily users of smokeless tobacco (76). Achia *et al* described tobacco use in females to be the highest in Lesotho (11%), followed by Uganda (6%) and Burkina Faso (4%), while Zimbabwe (0.9%) had the lowest use of tobacco. In males the prevalence of tobacco use was highest in Lesotho (34%), Zambia (24%) and Uganda (24%), and lowest in Ethiopia (17%) (77). Alcohol, acting both independently and synergistically with smoking, has been implicated in oral carcinogenesis (1,72). Acharya *et al* in 2012, made the hypothesis that a short duration of exposure to carcinogens is sufficient to incite malignant transformation. This hypothesis was made after the results of their study showed a significant difference in the duration of practising high-risk habits before a lesion developed. It was shown that in certain patients, a lesion developed after only 1 to 10 -years after first exposure to high-risk habits (20). The site of OSCC development within a field of cancerisation, is thought to be dependent on the type of risk factors that the patient had been exposed to. Potentially malignant disorders that arise secondary to betel quid usage, such as submucous fibrosis, develop in the area that the betel quid was placed. Most patients report placing the quid into the buccal sulcus and, hence, most cases of submucous fibrosis are found to involve the buccal mucosa (20). Similarly due to the pooling of alcohol and tobacco smoke on the floor of the mouth during consumption, these risk factors predispose to the development of OSCC in the floor of the mouth and the tongue (16,21,70,78,79). The lip is rarely involved by OSCC, with about 200 new cases a year reported by Pietersma *et al* in the Netherlands (80). Around 90% of OSCCs of the lip vermillion are found on the lower lip. However, according to Pieteresma *et al*, the proportion of lower lip OSCCs has decreased over the last 30 years while the amount of upper lip OSCCs has increased (80). People at a higher risk of developing OSCCs of the lip include males, Caucasians and people over the age of 50 years. The most important risk factor is a cumulative life-time exposure to sunlight, which is related to outdoor occupations and rural residency. Additional risk factors for SCC of the lip are smoking, low socioeconomic status and immune suppression (2,64,80). OSCCs of the lip have a good prognosis provided they are detected early and have a relatively infrequent rate of metastasis. However, a belief exists that OSCCs of the upper lip have a worse prognosis than those of the lower lip (81,82). While both Zitsch *et al* and Califano *et al* hypothesise that upper lip OSCC belongs to an aggressive class of disease, they provide no further explanation (81,82).

With regard to rare risk factors in the development of OSCC, JE Cleaver in 1968, described the defective repair replication of DNA in xeroderma pigmentosum (XP) (83). Kraemer *et al* in 1987 showed the cutaneous, ocular and neurological abnormalities in cases of XP (84). In 1994, Kraemer *et al* found malignant neoplasms to be present in 70% of XP patients with 57% of these patients presenting with either SCC or a Basal Cell Carcinoma (BCC) (85). Rosin *et al* in 1994 showed that XP patients are not only predisposed to skin cancers but also to neoplasms on the tip of the tongue (86). In a Zimbabwean study by Chidzonga *et al* in 2006, 50% of patients with SCC of the lip were living with albinism (87). Although both XP and albinism have been described in association with cutaneous SCCs, the prevalence of OSCC in these patients have not been well established.

Girod *et al* in France, found that the overall incidence of OSCC had decreased from 1995 to 2001, a decrease that was more pronounced in males than females. This study showed that the percentage of French females that smoked had doubled from 1995 to 2001. Girod *et al* also reported that the proportion of females who were not exposed to risk factors of tobacco and alcohol use was larger than unexposed males. They also found that younger females under the age of 45 years and older females over the age of 70 years had a greater chance of dying from OSCC than females between the ages of 46 and 69 years (33). OSCC has historically been reported as a disease of the elderly and was most commonly seen in males in their sixth to eighth decades of life. It used to be a disease that was rarely seen in patients under the age of 40 years, however, OSCC in young patients is increasingly reported in studies (16,20,21,88,89). Rikardsen *et al* and Pires *et al* reported 7% and 3% of their Norwegian and Brazilian cohort to be under the age of 40 years, respectively (16,21). In Norway, females and males are reported to be diagnosed at similar ages, as shown by Rikardsen *et al*, the mean age at diagnosis was 66 years for males and 68 years for females (16). Similarly, in Brazil, Pires *et al* found a mean age of 62 years (21). Acharya *et al* in India showed that of the total number of patients that were over 40 years, 30% were female while 14% of the patients under 40 were female (20). Pires *et al* as well as other authors have demonstrated that the mean age of males affected by OSCC is lower than the mean age of females (21,28,32).

In contrast, Effiom *et al* in Nigeria revealed a mean age of 45 years with a hugely significant 40 % of their patients being under the age of 40 (28). The male to female ratio of this Nigerian study was 1.4:1 with males being diagnosed at a younger age than females. According to the authors, this was due to males being exposed to carcinogenic risk factors at a younger age than females (28). Many other authors have attributed the rise of this disease in younger patients to the advent of HPV (41–44,46). In South Africa, Khammissa *et al* showed

that Blacks are generally diagnosed with OSCC at a younger mean age (around 57 -years) than Whites (around 61 -years) (10). Interestingly, for a developed country, very different results come from Northeastern Hungary, where Nemes *et al* found a male to female ratio of 5.2:1 in 2008, suggesting different risk factors to the rest of the world (23). It has been reported that the occurrence of OSCC in children and adolescents is extremely rare (90). Several authors hold the view that OSCCs in young patients (that is, under the age of 40 years) are more aggressive and have a worse prognosis than those in older patients (88–93). However, other literature finds that due to the low incidence of OSCC in younger patients, the available data is insufficient to make reliable inferences regarding the prognosis of OSCC in young patients (94). There has also been a suggestion that OSCC in young patients may be a distinct disease entity based on the different biological behaviours and aetiological factors by which younger patients are influenced (20).

Less than 4% of all oral malignancies are seen in patients younger than 40 years (95). OSCC has traditionally been called a disease of the elderly and is reported by many researchers to be most common in males in their sixth to eighth decades of life. However, its incidence in younger patients is reported to be increasing (20,88,89). OSCC in paediatric patients is believed to be aetiologically distinct from OSCC in adults as the classic risk factors most strongly implicated in OSCC such as tobacco smoking, alcohol consumption, and betel quid use, cannot be considered major risk factors, due to their limited duration of exposure in young patients. It has therefore been postulated that OSCC is dependent on the genetic sensitivity of the individual. Bodner *et al* found genetic sensitivity in young patients (18–39 years) who had tongue OSCC, with no known risk factors and they associated the development of OSCC in patients with systemic diseases or syndromes that predispose cancer development to genetic instability. The syndromes associated with genetic factors: xeroderma pigmentosum, ataxia telangiectasia, Bloom syndrome, colorectal cancer, Werner syndrome, and Fanconi's anaemia (95).

Important prognostic indicators that are known to affect regional metastasis and, therefore, disease outcome, include size of the primary tumour, site, T-stage, grade, depth of invasion, biological tumour markers, perineural invasion and patient compliance. The TNM classification of oral squamous cell carcinoma provides a basis for patient prognosis and therapeutic planning. Typically, T1-T2 lesions are often associated with a risk of regional metastasis, especially to lymph nodes, while several studies have shown a correlation between increasing tumour thickness and an increased risk of cervical metastasis. In patients diagnosed

with tumours at an advanced stage, there is a high occurrence of invasion to surrounding tissues, with lymph node and distant metastasis, and a high-risk of second malignancy during the patient's lifetime. Metastasis represents the leading cause of death from cancer (96).

An early diagnosis of OSCC remains the key element for the management of the disease, as the prognosis of OSCC is best in its early stages, especially well-differentiated OSCCs that have not metastasized (13). Clinicians should be aware that single or multiple ulcers, tumours, red or white plaques (particularly if any of these persist for more than two weeks) may be manifestations of a malignancy. In these cases a biopsy from the suspicious lesion is mandatory (97). However most OSCC's are at an advanced stage at the time of diagnosis. Factors that contribute to this include delay in seeking medical assistance, ignorance and lack of awareness of the clinical presentation of OSCC by both the patient and the attending health practitioner, and limited access to health care services (13,98). The mortality rate of OSCC has remained mostly unchanged for decades, with an average five-year survival rate of 50% (99). Most patients with advanced OSCC apparently succumb to the condition within 30 months of diagnosis (7,100). The prognostic evaluation of OSCC is based on the clinical TNM classification, however, this classification system must be supplemented by other reliable methods (101,102).

The Broder-Grading system evaluates the biological activity of OSCC and descriptively categorises it as well-, moderately- or poorly-differentiated. Broders' grades, however, do not correlate well with the prognosis of OSCC due to the fact that SCCs usually exhibit a heterogeneous cell population with probable differences in invasiveness and metastatic behaviour (101). In 1973, Jakobsson *et al* developed a multi-factorial malignancy grading system in order to obtain a more precise morphologic evaluation of the growth potential of SCCs in the head and neck region. To make the morphologic criteria more precise, Anneroth and Hansen modified the grading system developed by Jakobsson *et al.* for application to SCCs in the tongue and the floor of the mouth. This system is constituted by six histological variables of equal value in the determination of the grade of malignancy, three linked with tumour cell population (differentiation and the proliferation of mitotic figures), and the other three to the tumour-host relationship (the pattern and stage of invasion; and the type of cellular response) (103).

The degree of histologic differentiation, as well as the anatomic site of the lesion, plays a role in SCC evaluation and prognosis. Poorly-differentiated tumours, particularly from the lip, are

three times more likely to metastasize, and twice as likely to recur when compared to tumours that are well-differentiated (104). Perineural involvement (PNI) is an indicator of the aggressiveness of the tumour. Tumours with PNI have a greater risk of local recurrence (23%) compared to those without (9%); a poorer prognosis and a significant increase in mortality (105). PNI is thought to occur in approximately 14% of all SCCs arising in the head or neck (106). Similarly, invasion of capillary lymphatics signifies a more aggressive tumour and correlates with an increased incidence of metastasis, local recurrence, and disease-specific mortality (105). Additionally, OSCC metastasis occurs predominantly via local lymphatics and often deposits in the lymph nodes of the neck (107). The prognosis of OSCC is best when the primary tumour is small and there is no evidence of regional lymph node involvement or distant metastasis (17). The affected lymph nodes are generally firm and non-tender on palpation, however, if extra capsular spread into the surrounding connective tissue has occurred, they will be fixed and matted (14). The presence of extra capsular lymph node spread is associated with a high-rate of local and regional recurrence, distant metastasis and mortality (108). About 8% of patients with OSCC will have distant metastases at the time of diagnosis, most frequently to the lungs (14,108). SCCs of the lip, hard palate and maxillary gingiva rarely metastasize to lymph nodes, they usually run a relatively indolent course and have a relatively favourable prognosis, while SCC of the tongue, floor of the mouth and the mandibular gingiva often metastasize to regional lymph nodes and are more aggressive with a poorer prognosis (17).

The literature on OSCCs around the world is generally readily available and, therefore, the clinicopathological characteristics and trends of the disease can be compared and contrasted by different countries and population groups. The early detection of OSCCs is essential for early treatment. Education on the disease could, in a best case scenario, lead to prevention. A thorough understanding of what makes a group high-risk is therefore vital in order to make this change. In South Africa, very little literature has been dedicated to the clinicopathological characterisation of OSCCs between the male and female genders. In 2011, Ndui Mary, in her thesis, looked at the epidemiology of oral cancer in South Africa over the period 1996 to 2002. However, the study included the tonsils and oropharynx, which does not limit their findings specifically to the oral cavity (109). Khammissa *et al* in 2014 studied OSCC in a South African sample which had an emphasis on race and ethnicity. Their study spanned the seven-year period 1995 to 2002 (10), and perused data that could now be considered outdated. In 2012, Abram *et al* researched the epidemiology of OSCC in South Africa for the five year period 1997-2001. Their results were based on the incidence of both oral and oropharyngeal

cancers without delving into the clinicopathological characteristics of OSCC in particular (110). The data used for that study was collected from the national cancer registry and could also be considered outdated. Ayo-Yusuf *et al* in 2013, reported on the trends and ethnic disparities in oral and oro-pharyngeal cancers in South Africa using data from the years 1992 to 2001. However, they grouped oral cancers and oro-pharyngeal cancers together and did not characterise oral cancers in particular (6). Therefore, although South African literature on OSCCs exists, there is a paucity of information available for the characteristics and trends of OSCCs in male and female South Africans. South Africa is a unique hub of cultural and ethnic diversity and offers the opportunity to study the characteristics of OSCC in a population where people are different and the risk factors may be different to those seen internationally. South Africa is a country where conditions like albinism and xeroderma pigmentosum (XP) predispose individuals to OSCC at young ages. Due to the high rate of immunosuppression by HIV, the South African population may present diseases like OSCC differently and more frequently than other countries, both on the continent and internationally. The way in which OSCC presents in a South African population influences the way in which it is subsequently managed. OSCCs that are well managed have a better prognosis and thus the patient will enjoy a better quality of life. The country will benefit from a decreased disease burden and save costs that are currently allocated to the treatment of OSCC.

Given the assumed increased use of alcohol and tobacco by females over the years, coupled to the overarching burden of HIV; we set out to investigate whether this change in behaviour could be associated with an increasing proportion of OSCC in females. The possibility that the presentation of OSCCs may be different in males and females was explored and we sought to describe the clinicopathological characteristics and trends of OSCC in both genders using recent data.

1.2 Aims and objectives

The aim of this study was to conduct a comparative analysis of the clinicopathological characteristics and trends of OSCC between males and females diagnosed at the Department of Oral Pathology, University of the Witwatersrand over the ten-year period 2004 to 2013.

The objectives are listed as follows:

1. To determine the proportion of females and males with OSCC over a ten year period.
2. To determine the prevalence of known risk factors in the study group.
3. To determine whether significant differences exist with respect to the prevalence of risk factors for the development of OSCC in males and females.
4. To determine the association between the site of OSCC and the reported risk factors involved in females and in males.
5. To determine the proportion of “well”, “moderately”, and “poorly-differentiated” OSCC diagnosed over the 10 year study period in males and females.

CHAPTER TWO:

Methods and materials

2.1 Study design

This study was a retrospective, descriptive and comparative study.

2.2 Study and sample selection

The study population consisted of records of OSCC cases¹, fitting the inclusion criteria, over the ten-year period, 2004 to 2013. These records were collected in the form of histopathology reports from the archives of the Department of Oral Pathology, University of the Witwatersrand and represented cases predominantly from Johannesburg and surrounding areas.

2.2.1 Inclusion criteria

The inclusion criteria comprised histopathology reports, from the years 2004 to 2013, specimens confirmed to be OSCC by the Department of Oral Pathology.

2.2.2 Exclusion criteria

The reports that were excluded were those that diagnosed SCCs at sites outside of the oral cavity. (The boundaries of the oral cavity are represented in the mouth chart found in Appendix A). Reports of carcinoma-in-situ were also excluded.

2.3 Sample size

The sample size of 1049 was determined by considering the following key questions:

- (1) What percentage of females was diagnosed with OSCC each year?
- (2) What was the prevalence of known risk factors for OSCC in females versus males?

The total available data was estimated, at the time, to be over 1,000 histopathology reports. That is, 100 hundred cases were thought to be diagnosed by the Department of Oral Pathology every year over the ten year period included in this study.

¹ These are records of OSCC cases generated from patients that were seen in the clinic at some point.

For (1), the estimation of a 50% proportion (worst-case in terms of sample size) at the 95% confidence level, with a sample size of 100, could be done with 9.8% precision. While larger than the 5% precision, for which is typically aimed, it was considered adequate for a study of this nature (and is limited by the available data).

For (2), the comparison was conducted using Fisher's exact test. Illustrative sample size calculations showed that to determine the differences in prevalence of a given risk factor between males and females of 50% versus 60, 70 or 80% at the 5% significance level with 80% power required a sample size of 808, 204 and 88 respectively. Similarly, determining differences in prevalence of 10% versus 20, 30 or 40% at the 5% significance level with 80% power required sample size of 428, 138 and 72 respectively. The anticipated sample size of around 1,000 was thus adequate for this objective.

The sample size for proportions was determined using the formula:

$$n = \frac{Z^2 P(1 - P)}{d^2}$$

where "n" represented the sample size, "Z" was the z-statistic for the chosen level of confidence, "P" was the expected prevalence or proportion and "d" represented precision (111).

The sample size calculations for Fisher's exact test were carried out in G*Power (112).

2.4 Method

The Department of Oral Pathology houses hard copies of all histopathology reports reported by the Department.

Over ten thousand histopathology reports were authorised by the Department during the years 2004 to 2013, all of which were perused during the data collection stage of this study.

Of these, 1049 reports had a confirmed a diagnosis of OSCC. These were extracted from the archives according to the inclusion and exclusion criteria mentioned above. Each report included a summary of the clinical requisition form and the histopathology report.

Each report was allocated a study identification number; and demographic, clinical and histopathological data were entered into the data collection sheet. (The data collection sheet is available in appendix B).

The variables were categorised and recorded as follows:

1. The year in which the report was authorised.
2. The exact age of the patient as stated on the report. (The ages were later divided into decades.)
3. The gender of the patient was captured as either male or female.
4. The race of the patient was categorised according to the census of South Africa, 2013, into Black/African, White, Coloured, Indian/Asian and other (113).
5. Any risk factors that were available on the report were categorised according to Warnakulasuriya *et al* in 2009, as tobacco smoking, tobacco chewing, alcohol use and other. These categories are well-established risk factors for the development of OSCC (2). The “other” category was used by noting down every condition that was mentioned in the clinical history.
6. The patients’ history of any previous cancer as per what was available on the report.
7. The site of the lesion was categorised according to the mouth chart by Crispian Scully in the textbook “Oral and Maxillofacial Medicine” (114). The sites used were upper lip, lower lip, gingiva, buccal mucosa, hard palate, floor of mouth, dorsal surface of the tongue, ventral surface of the tongue, lateral surface of the tongue and retromolar area.
8. Metastasis of the tumour was marked if it was mentioned in the report.
9. Keratinisation of the tumour was marked.
10. The histopathological degree of differentiation was categorised according to the International Classification of Diseases (ICD) for Oncology into the following three categories: well-differentiated, moderately-differentiated or poorly-differentiated (115).

Data that was missing from histopathology reports, such as differentiation and keratinisation, was determined by review of the corresponding haematoxylin and eosin (H&E) slides which were drawn and reviewed by a specialist oral pathologist while the primary researcher observed. However, not all the H&E slides were available and those cases that could not be evaluated were recorded as having missing data. This evaluation was performed in the Department of Oral Pathology at the Wits Oral Health Centre.

2.5 Data capture and analysis

The descriptive analysis of data was carried out by summarising categorical variables by frequency and percentage tabulation; they were also illustrated by means of bar charts. The continuous variables were summarised by the mean, standard deviation, median and interquartile range. Their distribution was illustrated by histograms.

The percentage of females in the study group were estimated (together with the 95% confidence interval), overall and per year. The trend of the percentage female composition of the study group over the years was tested using the Cochran-Armitage test for trend.

The Fisher's exact test was used to assess the relationships between gender and known risk factors. The strength of the associations was measured by the phi coefficient.

Similarly, Fisher's exact test was used to determine the association between site and gender, and site and risk factor. Data analysis was carried out using SAS (version 9.4 for Windows). The 5% significance level was used. *In other words, p -values <0.05 indicate significant results.*

2.6 Ethical considerations

The protocol for this project was approved by the Faculty of Health Sciences; and the ethical clearance was granted by the Human Research Ethics Committee of the University of the Witwatersrand (Appendices C and D).

CHAPTER THREE:

Results

3.1 OSCC cases over the ten-year period 2004 to 2013

A total of 1049 OSCC cases were evaluated for this study, a summary of the complete results is tabulated in Table 3.1. All H&E sections (slides) reviewed in this study were of good quality and readable as there were no signs of fading.

Figure 3.1. shows the number of cases that presented with OSCC each year over the ten year period 2004 to 2013. The number of cases appears to fluctuate over the ten years included in this study, however; on average, the number of OSCC cases was lower in 2013 than it was in 2004.

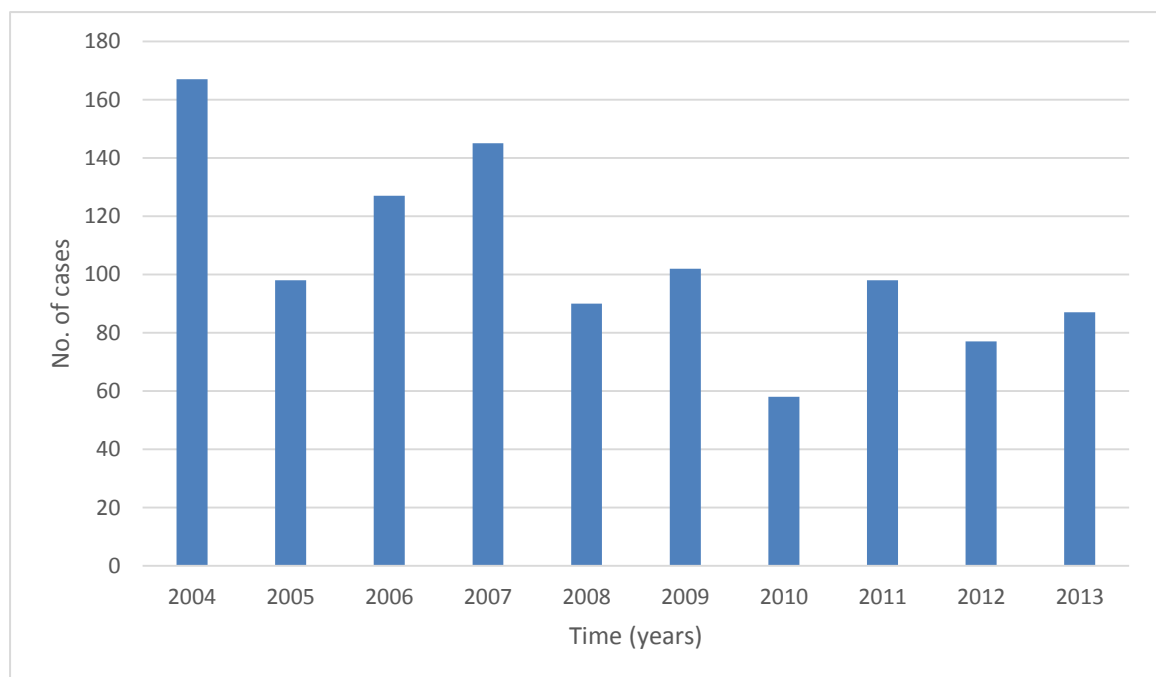


Figure 3.1 The number of cases who presented with OSCC over the ten year period.

Table 3.1 The demographic and histopathological features of all OSCC cases evaluated in this studied sample. Note that the number of cases for each parameter includes the number of reports that contain precise available information.

Parameter	Number of cases	Percentage
Gender (n = 1038)		
Males	743/1038	71.6 %
Females	295/1038	28.4 %
Unspecified ²	11/1049	1.0 %
Age (n = 1018)		
40 years and under	74/1018	7.3 %
41 to 60 years	541/1018	53.1 %
61 to 80 years	377/1018	37.0 %
Over 80 years	26/1018	2.6 %
Unspecified	31/1049	3.0 %
Race (n = 58)		
Black/African	43/58	74.1 %
White	12/58	20.7 %
Coloured	2/58	3.4 %
Indian/Asian	1/58	1.7 %
Unspecified	991/1049	94.4 %
Risk factors (n = 315)		
Tobacco smoking	208/315	66.0 %
Tobacco chewing	1/315	0.3 %
Alcohol consumption	54/315	17.1 %
Xeroderma pigmentosum	2/315	0.6 %
Sun exposure	3/315	1 %
Oral snuff	3/315	1 %
HIV	24/315	7.6 %
Albinism	7/315	2.2 %
Other conditions	13/315	4.1 %
Not stated	734/1049	70 %
Site (n = 1653)		
Upper lip	24/1653	1.5 %
Lower lip	133/1653	8.0 %
Gingiva	146/1653	8.8 %
Buccal mucosa	78/1653	4.7 %
Hard palate	83/1653	5.0 %
Floor of mouth	306/1653	18.5 %
Dorsal surface of the tongue	219/1653	13.2 %
Ventral surface of the tongue	246/1653	14.9 %
Lateral border of the tongue	333/1653	20.1 %
Retromolar area	85/1653	5.1 %
History of previous cancer (n = 37)		
History of previous cancer	37/1049	3.5 %
Not stated	1012/1049	96.5 %
Metastasis (n = 15)		
Metastasis	15/1049	1.4 %
Not stated	1034/1049	98.6 %
Differentiation (n = 1015)		
Well-differentiated	32/1015	3.2 %
Moderately-differentiated	835/1015	82.3 %
Poorly-differentiated	148/1015	14.6 %
Unspecified	34/1049	3.2 %
Keratinisation (n = 853)		
Keratinised	853/1049	81.3 %
Unspecified	196/1049	18.7 %

² The terms “unspecified” and “not stated” refer to data that was not available on histopathology reports.

3.2 Gender

The majority of cases (71.6 %, n = 743) diagnosed with OSCC over the ten-year period were male and less than half of the total number were female (28.4 %, n = 295), resulting in an overall male to female ratio of 2.5:1 (Table 3.2.).

Table 3.2 A comparison between the numbers of each gender that presented with OSCC.

Gender	N	%
Female	295	28.4
Male	743	71.6
Total	1038	

There was a significant increase in the percentage of females affected by OSCC over the ten year period (Figure 3.2.). This increase in the proportion of females over time is confirmed by the Cochran-Armitage test for trend ($p < 0.0001$).

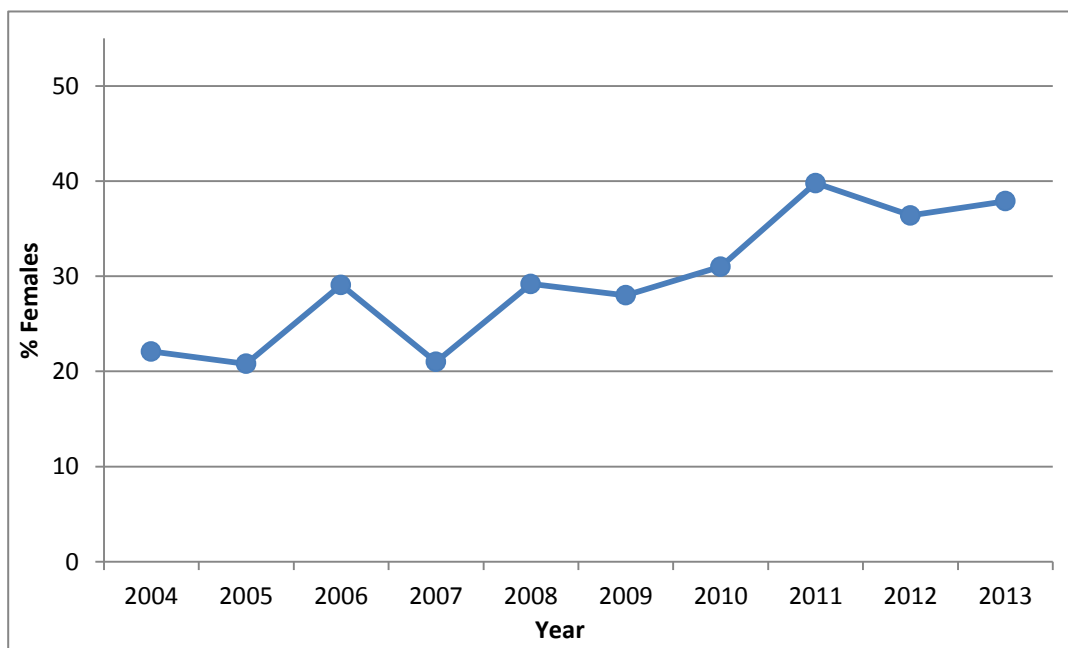


Figure 3.2 A trend in the percentage of females within those affected by OSCC, overall and per year.

3.3 Age

Figure 3.3. shows the age distribution of cases diagnosed with OSCC from 2004 to 2013 and Table 3.3. shows the age distribution according to gender. The highest male to female ratio was seen in the 41 to 50 age group. However, the highest number of cases diagnosed with OSCC were found to be between 51 and 60 years old. The mean age of OSCC cases was 57.3 years while the age of the total number of cases ranged between 2 and 93 years. The standard deviation was found to be 12.1 years. Cases under the age of 40 years amounted to 7.3 %. Of the total number of reports, 3.0 % did not state the age. Figure 3.4. shows that, overall, males (mean age of 56.7 years) presented with OSCC at a younger age than females (mean age of 58.7 years).

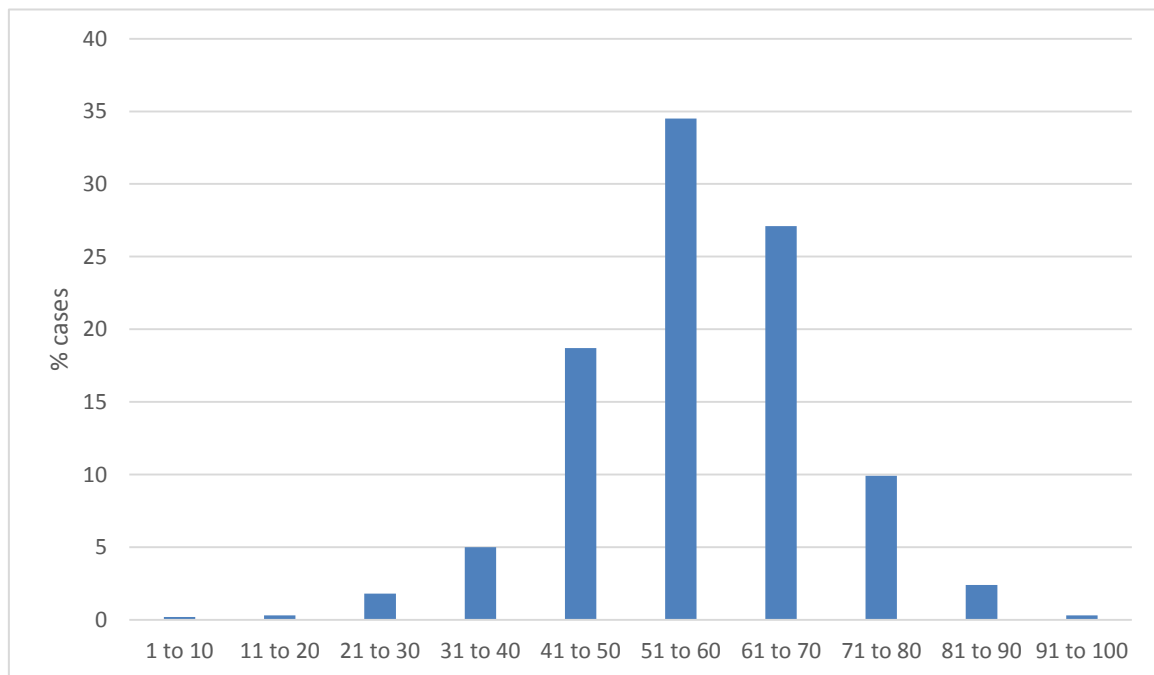


Figure 3.3 The percentage of cases diagnosed with OSCC according to age groups.

Table 3.3 Age distribution according to gender.

Age (years)	Male	Female	Male : Female	Total	%
1 to 10	0	2	0 : 2	2	0.2
11 to 20	1	2	1 : 2	3	0.3
21 to 30	8	9	1 : 1,1	17	1.7
31 to 40	37	13	2.8 : 1	50	4.9
41 to 50	154	34	4.5 : 1	188	18.5
51 to 60	255	92	2.8 : 1	347	34.1
61 to 70	187	87	2.1 : 1	274	26.9
71 to 80	64	36	1.8 : 1	100	9.8
81 to 90	13	12	1.1 : 1	25	2.5
91 to 100	1	2	1 : 2	3	0.3
Total				1009	

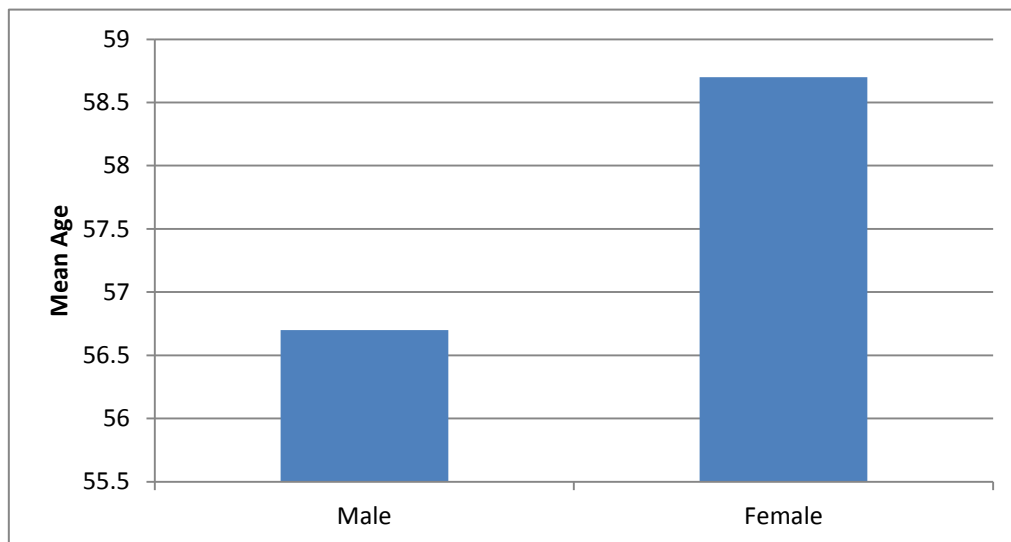


Figure 3.4 A comparison between the mean age at diagnosis of males and females.

3.4 Race

The race of cases diagnosed with OSCC was a much pre-empted finding , however, as seen in Figure 3.5., 94.4 % of histopathology reports did not acknowledge the patient's race and were, thus, recorded as having missing data. Of the 58 reports that did state the race, 74.1 % (n=43) were Black/African; 20.7 % (n=12) were White; 3.4 % (n=2) were Coloured and 1.7 % (n=1) was Indian/Asian.

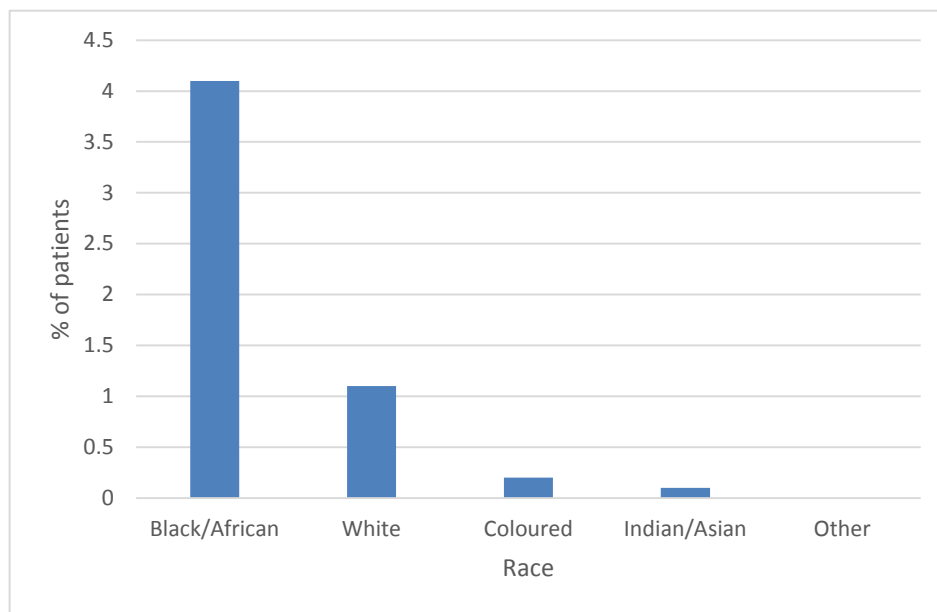


Figure 3.5 The percentage of cases diagnosed with OSCC in each race group.

3.5 Risk factors

Established risk factors for the development of OSCC are presented in Figure 3.6. No risk factors were reported in 70.0 % (n = 734) of all perused histopathology reports, presumably as a consequence of inadequate provision of information on the clinical requisition form. Tobacco smoking was the most common habit at 66.0 % (n = 208); tobacco chewing was practised by 0.3 % (n = 1) and 17.1 % (n = 54) consumed alcohol. Of the total number of reports, concurrent tobacco smoking and alcohol consumption amounted to 5.1 % (n = 54). Albinism was reported in 2.2 % (n = 7); a history of oral snuff use presented in 1.0 % (n = 3) and 1 % (n = 3) showed a history of sun exposure. Xeroderma pigmentosum occurred in two cases amounting to 0.6 % (n = 2).

Figure 3.7. shows that the percentage of female smokers had increased since 2004 and had peaked in 2011. The increasing number of females is shown against the increasing number of female smokers in Figure 3.8. The “other” category was used for diseases and conditions that are not established in the development of OSCC; they accounted for 4.1 % (n=13) of cases and are represented in Figure 3.9. The “other” category included 1.3 % (n = 4) cases of tuberculosis; 1.3 % (n = 4) cases of hypertension; 1 % (n = 3) cases of diabetes; 1 case of hepatitis C and 1 case of mental retardation. HIV-positive cases made up 7.6 % (n=24) and is discussed separately.

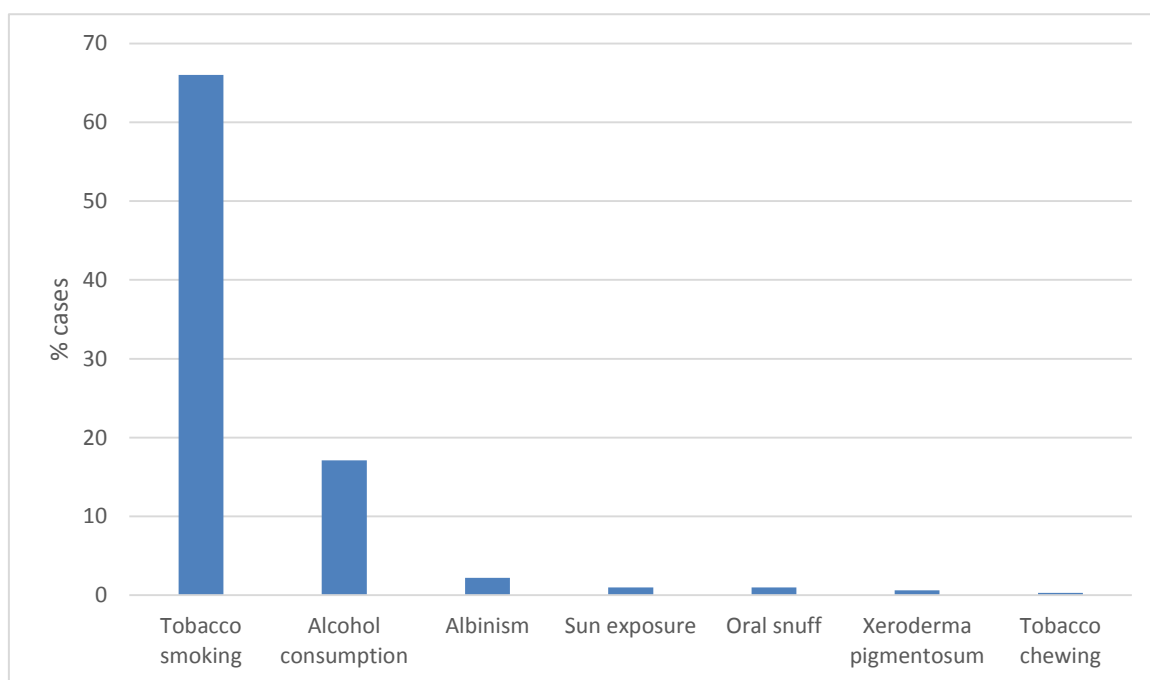


Figure 3.6 Risk factors in the development of OSCC.

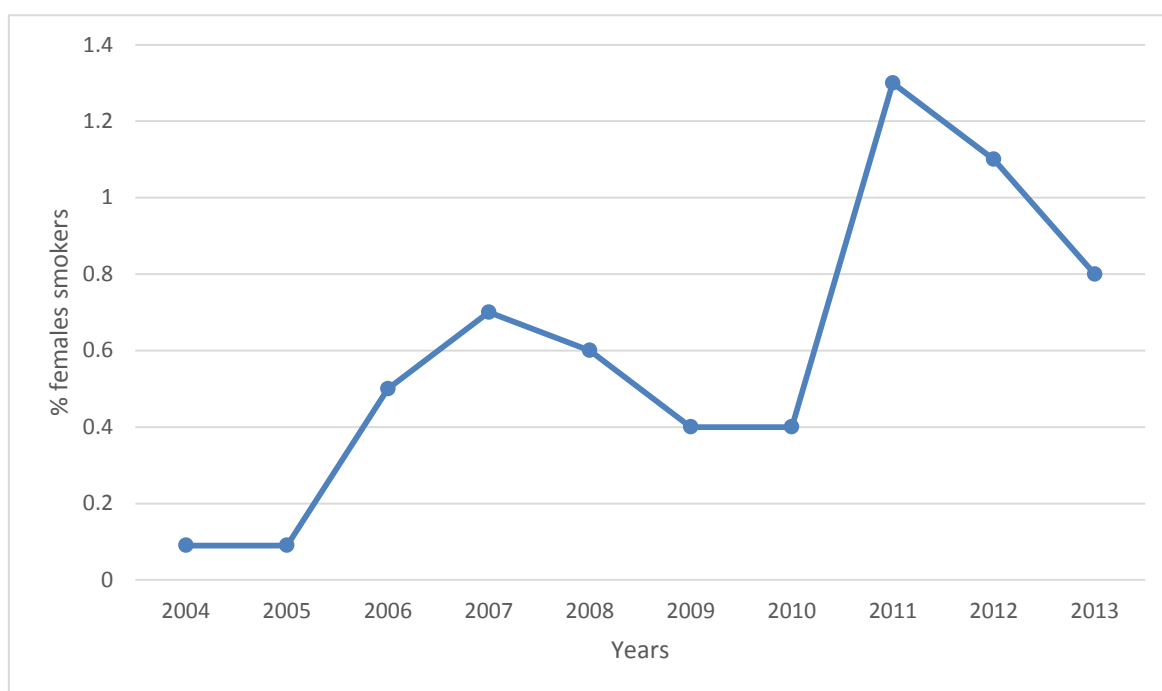


Figure 3.7 The trend of female smokers over a ten year period.



Figure 3.8 The number of female cases versus the number of female smokers over the ten-year period.

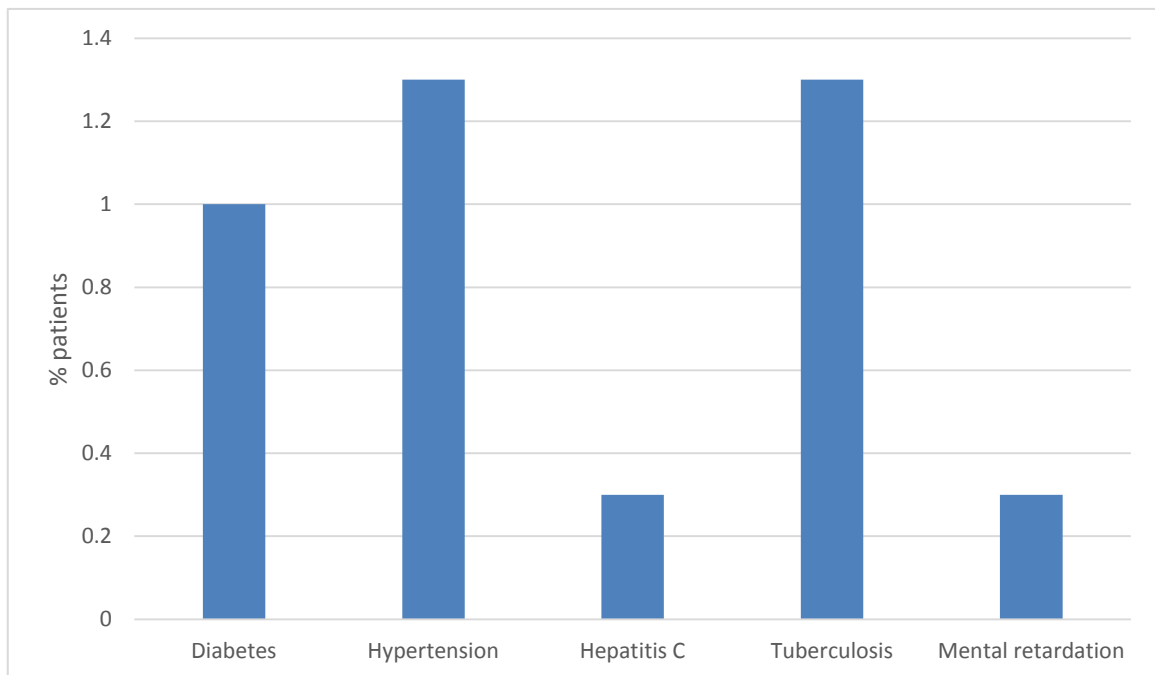


Figure 3.9 Other diseases and conditions.

The associations found between gender and known risk factors for OSCC are tabulated in Table 3.4. Only the risk factors “smoking” and “alcohol use” were analysed, since the overall prevalence of “tobacco chewing” (0.3 %; n=1) was too low for further analysis (P-values < 0.05 indicate significant results). There was no significant association found between gender and “smoking” (p = 0.73) or “alcohol use” (p = 0.12), suggesting that risk factors traditionally associated with males are as prevalent as females in this study group.

Table 3.4 Associations between gender and known risk factors.

	Female		Male		p-value for H0: no significant association with gender
	n	%	N	%	
	295		743		
Tobacco smoking	61	20.7	146	19.7	0.73
Alcohol consumption	10	3.4	44	5.9	0.12
Tobacco chewing	0	0	1	0.1	-

3.5.1 HIV

HIV-positive cases accounted for 2,3 % (n = 24) of the total sample. Figure 3.10. shows that the majority (62.5 %, n = 15) of HIV-positive cases were male and 37.5 % (n = 9) were female.

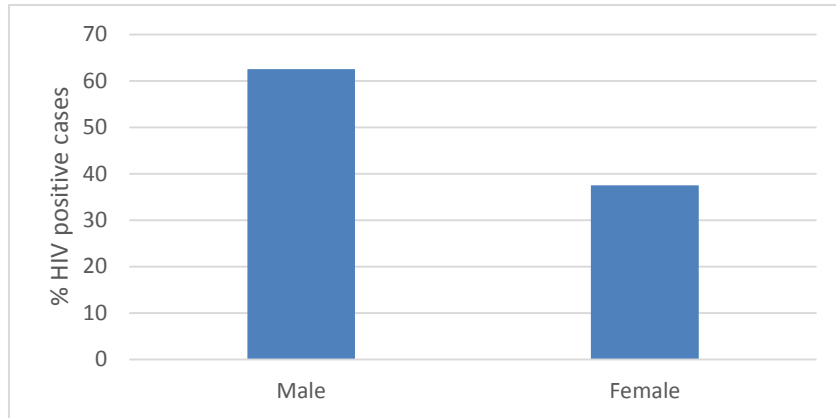


Figure 3.10 The gender of HIV-positive cases that presented with OSCC

The age range of HIV-positive cases with OSCC is shown in Figure 3.11. None of the HIV-positive cases were under the age of 10 years; cases between the ages of 11 and 20 accounted for 4.2 % (n = 1), whilst 87.5 % (n = 21) were between the ages of 31 and 60 years and 8.3 % (n = 2) were between 61 and 70 years of age.

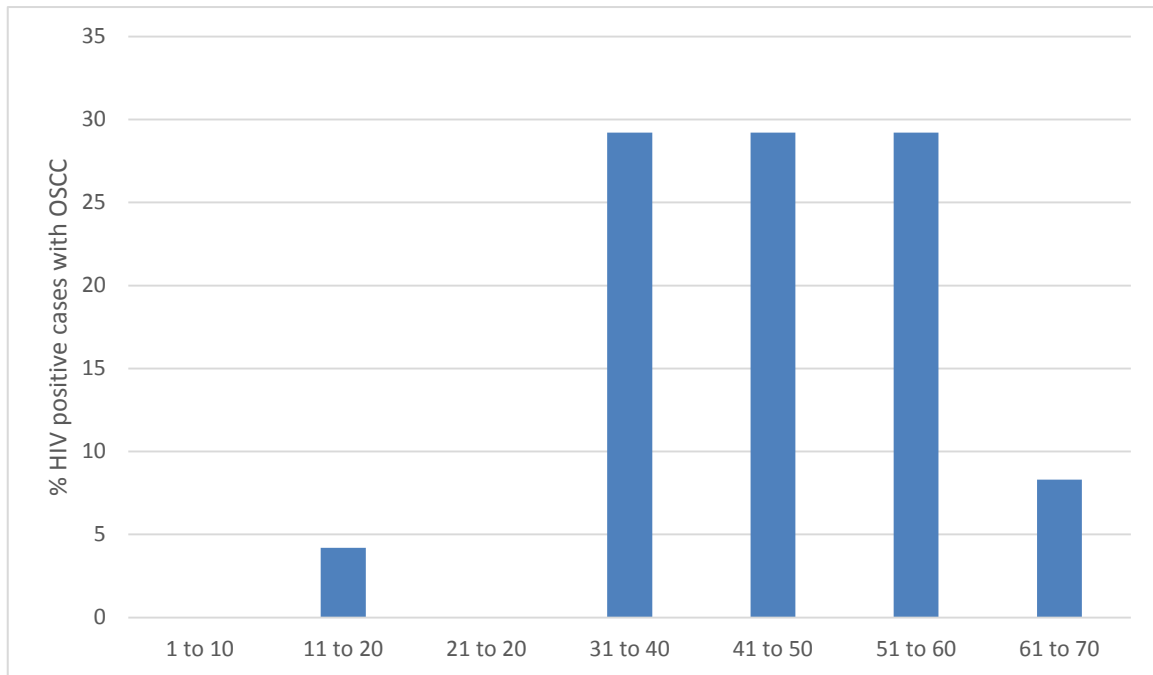


Figure 3.11 The age range of HIV-positive cases that presented with OSCC.

The affected sites in the HIV-positive cases were as follows: the lower lip was affected in 25.0 % (n = 6), the hard palate in 25.0 % (n = 6), the lateral border of the tongue in 20.8 % (n = 5), the gingiva in 16.7 % (n = 4), the dorsal surface of the tongue in 16.7 % (n = 4), the buccal mucosa in 12.5 % (n = 3), the ventral surface of the tongue in 12.5 % (n = 3), the floor of the mouth in 8.3 % (n = 2), and the retromolar area in 4.2 % (n = 1). The upper lip was not affected in any HIV-positive cases (Figure 3.12.).

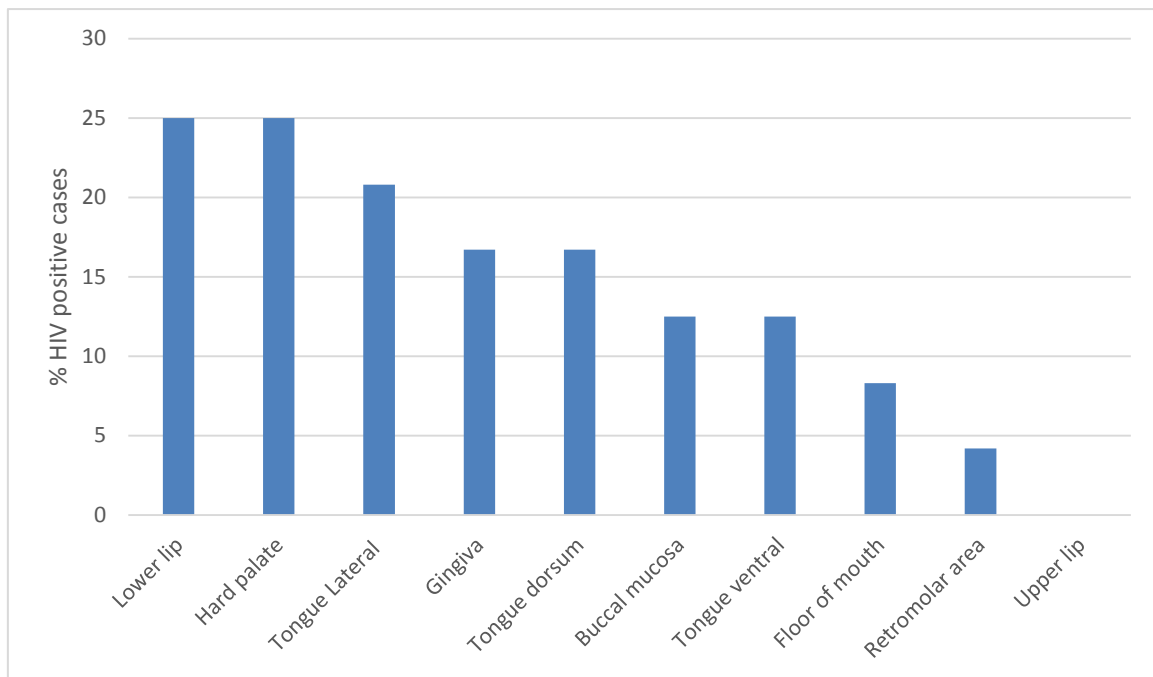


Figure 3.12 Sites of OSCC involvement in HIV-positive individuals

Of the HIV-positive cases, 87.5 % (n = 21) presented with moderately-differentiated OSCC and 12.5 % (n = 3) with poorly-differentiated OSCC (Figure 3.13.). None of the HIV-positive individuals presented with well-differentiated OSCC.

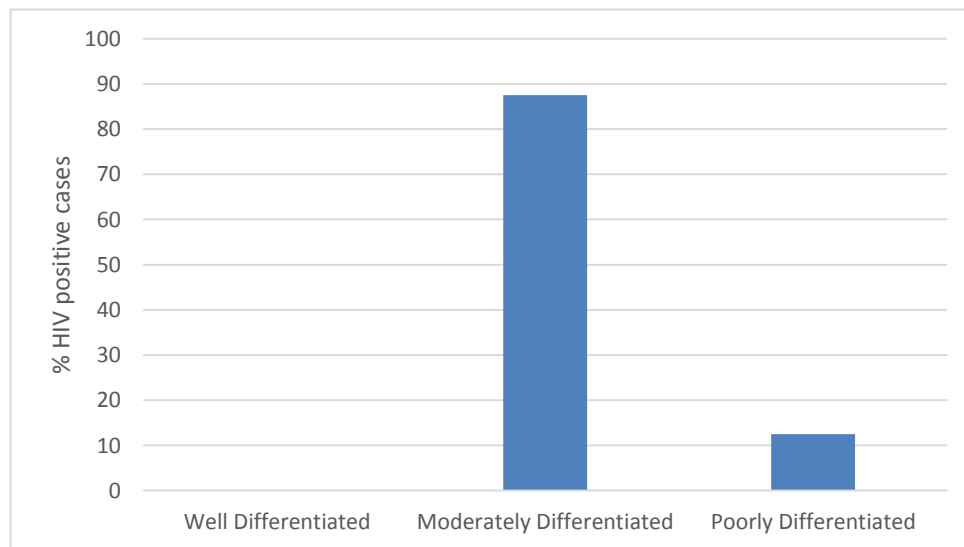


Figure 3.13 The degree of differentiation seen in HIV-positive cases.

3.6 Site of involvement

The most common site of OSCC involvement was the lateral border of the tongue at 20.1 % (n = 333) followed by the floor of the mouth at 18.5 % (n = 306). The least affected site was the upper lip at 1.5 % (n = 24) (Figure 3.14.). However, the prevalence of OSCC of the upper lip was higher in females (5.1 %) than in males (1.2 %) and was statistically significant (p = 0.0007) (Table 3.5.).

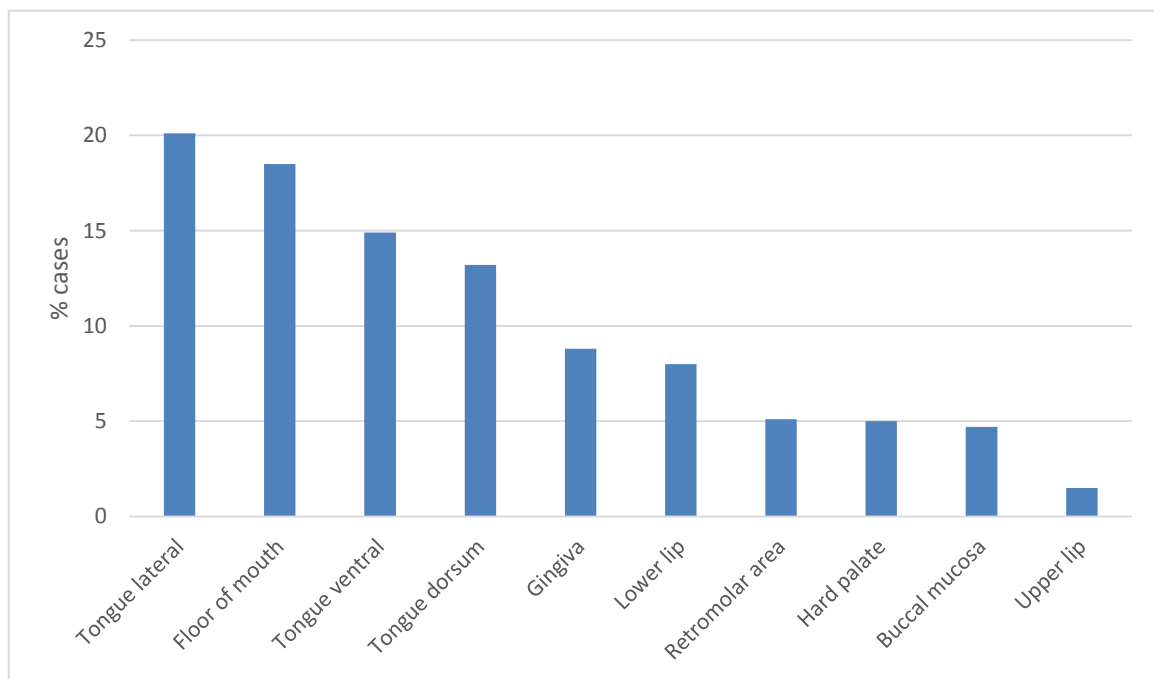


Figure 3.14 The sites of OSCC involvement

Smokers showed significant differences in the prevalence of OSCC at the floor of mouth, lower lip, retromolar area and upper lip. Smoking was associated with a higher prevalence of OSCC at the floor of mouth and retromolar area when compared to non-smokers, and a lower prevalence of OSCC at the lower lip and upper lip compared to non-smokers. The associations are shown in Table 3.6. and Figure 3.15. The prevalence of OSCC at the lower lip was higher in non-users of alcohol (13.3 %) when compared to users of alcohol (1.9 %) (p = 0.010) (Table 3.6.).

Table 3.5 A comparison between the sites of involvement in males and females.

Sites of involvement	Gender				<i>p</i> -value for H0: no significant association with gender
	Female		Male		
	n = 295		n = 743		
	n	%	N	%	
Lateral border of the tongue	97	32.9	233	31.4	0.65
Floor of Mouth	74	25.1	230	31.0	0.07
Ventral surface of the tongue	63	21.4	181	24.4	0.33
Dorsal surface of the tongue	60	20.3	157	21.1	0.80
Gingiva	46	15.6	99	13.3	0.37
Lower Lip	38	12.9	94	12.7	0.92
Retromolar Area	17	5.8	67	9.0	0.10
Hard Palate	25	8.5	55	7.4	0.61
Buccal Mucosa	28	9.5	48	6.5	0.11
Upper Lip	15	5.1	9	1.2	0.0007

Table 3.6 A comparison between the sites of OSCC involvement and risk factors

Sites of involvement	Risk factor: Smoking		<i>p</i> -value for H0: no significant association with smoking	Risk factor: Alcohol		<i>p</i> -value for H0: no significant association with alcohol
	n = 208			n = 54		
	n	%		n	%	
Lateral border of the tongue	77	37.0	0.08	22	40.7	0.18
Floor of mouth	77	37.0	0.0064	19	35.2	0.36
Ventral surface of the tongue	46	22.1	0.65	12	22.2	> 0.99
Dorsal surface of the tongue	36	17.3	0.18	10	18.5	0.73
Gingiva	30	14.4	0.82	10	18.5	0.31
Lower lip	13	6.3	0.0015	1	1.9	0.010
Retromolar area	26	12.5	0.0015	6	11.1	0.44
Hard palate	11	5.3	0.15	4	7.4	> 0.99
Buccal mucosa	17	8.2	0.66	3	5.6	0.79
Upper lip	0	0.0	0.0078	0	0.0	0.63

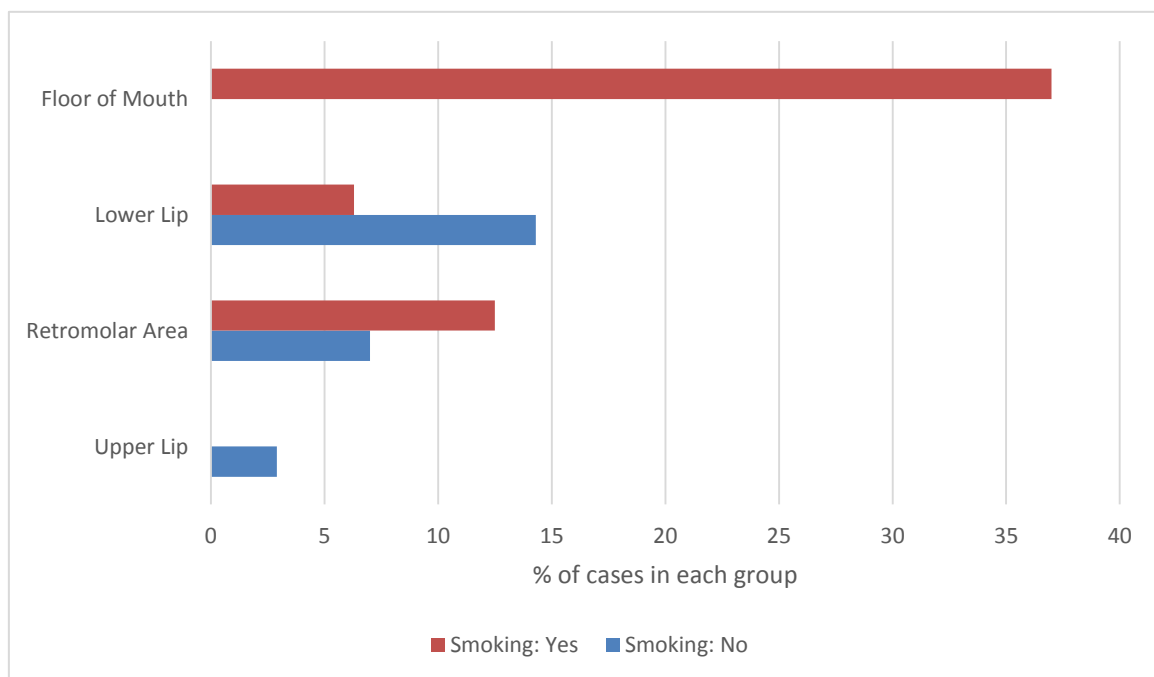


Figure 3.15 Sites of involvement associated with smoking and non-smoking cases

3.7 Metastasis and history of previous cancer

A history of previous cancer was documented as per clinical details that were provided. Out of the total number of reports, 3.5% (n = 37) reports mentioned a history of cancer while the remaining reports either stated that there was no history of cancer or did not mention this at all. Metastases were present in 1.4 % (n = 15) cases. None of the reports differentiated between regional and distant metastasis. Males showed a higher incidence of previous cancer and metastasis than females as shown in (Table 3.7.).

Table 3.7 Metastasis and history of previous cancer in males and females

	History of previous cancer	Metastasis
Male	24 (2.3%)	11 (1.0%)
Female	13 (1.2%)	4 (0.4%)
Total	37 (3.5%)	15 (1.4%)

3.8 Keratinisation and differentiation

Keratinisation of OSCCs was confirmed by evaluation of H&E slides. Of the total number of cases, 81.3% (n = 853) presented with keratinisation.

The various degrees of differentiation are shown in Figure 3.16. Well-differentiated OSCCs made up 3.2 % (n = 32) of cases; 82.3 % (n = 835) were moderately-differentiated and 14.6 % (n = 148) showed poor differentiation. Cases that could not be evaluated due to the lack of availability of the relevant H&E slides made up 3.2 % (n = 34).

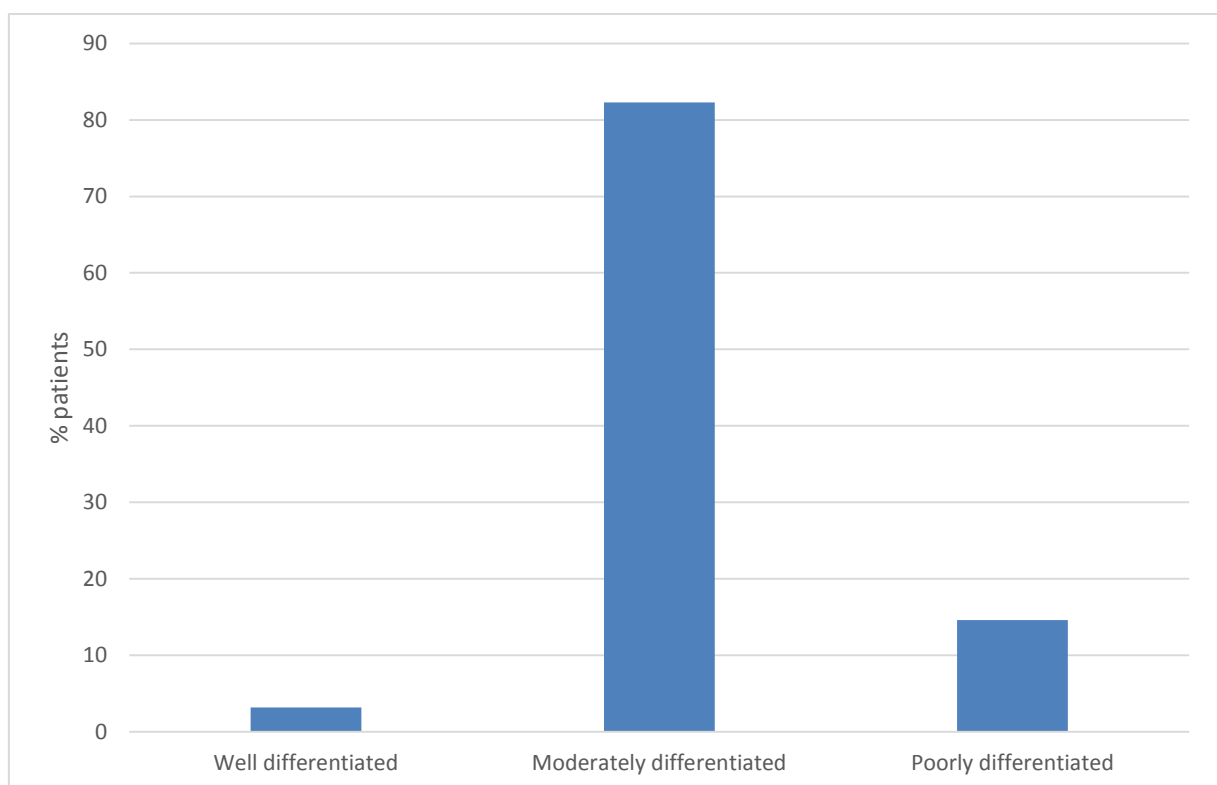


Figure 3.16 The percentage of OSCC cases as a factor of the degree of differentiation.

Table 3.8. shows that moderately-differentiated OSCCs were the most common type of differentiation overall. Moderately-differentiated OSCCs were most prevalent in males between the ages of 51 and 60 years, while well-differentiated OSCCs were most common in younger males between 41 and 50 years and poorly-differentiated OSCCs in older males between the ages of 61 and 70 years.

Table 3.8 The differentiation of OSCCs between the genders and based on age

Age group (years)	Well-differentiated		Moderately-differentiated		Poorly-differentiated		Total
	Male	Female	Male	Female	Male	Female	
0 to 10	0	0	0	1	0	1	2 (0.2 %)
11 to 20	0	0	1	2	0	0	3 (0.3 %)
21 to 30	1	1	6	8	1	0	17 (1.7 %)
31 to 40	2	1	29	10	5	2	49 (5.0 %)
41 to 50	8	0	124	25	16	8	181 (18.5 %)
51 to 60	3	3	216	76	32	11	341 (34.8 %)
61 to 70	5	4	143	72	33	6	263 (26.8 %)
71 to 80	1	2	48	27	14	5	295 (30.0 %)
81 to 90	0	0	10	8	3	3	24 (2.5 %)
91 to 100	0	0	1	2	0	0	3 (0.3 %)
Total	20	12	578	229	104	54	

The most common site of involvement in both males and females was the lateral border of the tongue (20.1 %, n = 324). Although both genders were affected, males (n = 228) showed more lateral border of the tongue lesions than females (n = 96), with a 2.4:1 male to female ratio. Most of these lesions were moderately-differentiated (n = 269). The least common site of involvement was the upper lip which was affected more frequently in females (n = 15) than in males (n = 9) with a 1:1.7 ratio. Most upper lip OSCCs were moderately-differentiated (n = 18). Most of the well-differentiated OSCCs were found on the lower lip (n = 21) while most poorly-differentiated OSCCs were on the lateral surface of the tongue (n = 51). (Table 3.9.)

Table 3.9 Site, gender and degrees of differentiation of OSCC.

Site distribution	Gender		Male: Female	Histological subtype			Total
	Male	Female		Well-differentiated	Moderately-differentiated	Poorly-differentiated	
Upper lip	9	15	1:1.7	2	18	4	24
Lower lip	90	37	2.4:1	21	99	7	127
Gingiva	98	46	2.1:1	2	112	30	144
Buccal mucosa	48	28	1.7:1	1	63	12	76
Hard palate	53	25	2.1:1	0	65	13	78
Floor of mouth	220	74	2.3:1	3	251	40	294
Dorsal surface of the tongue	153	58	2.6:1	1	171	39	211
Lateral border of the tongue	228	96	2.4:1	4	269	51	324
Ventral surface of the tongue	175	63	2.8:1	1	197	40	238
Retromolar area	63	16	3.9:1	0	65	14	79

Well-differentiated OSCCs made up 3.5 % (n = 7) of cases where tobacco smoking was a risk factor, moderately-differentiated tumours made up 87 % (n = 177) and poorly-differentiated tumours made up 8.9 % (n = 18). One case involving tobacco chewing was documented and the OSCC was recorded as being moderately-differentiated. In cases where alcohol consumption was a risk factor, 3.8 % (n = 2) represented well-differentiated OSCCs, 87 % (n = 45) showed moderate differentiation and 9.6 % (n = 5) showed poor differentiation (Figure 3.17.).

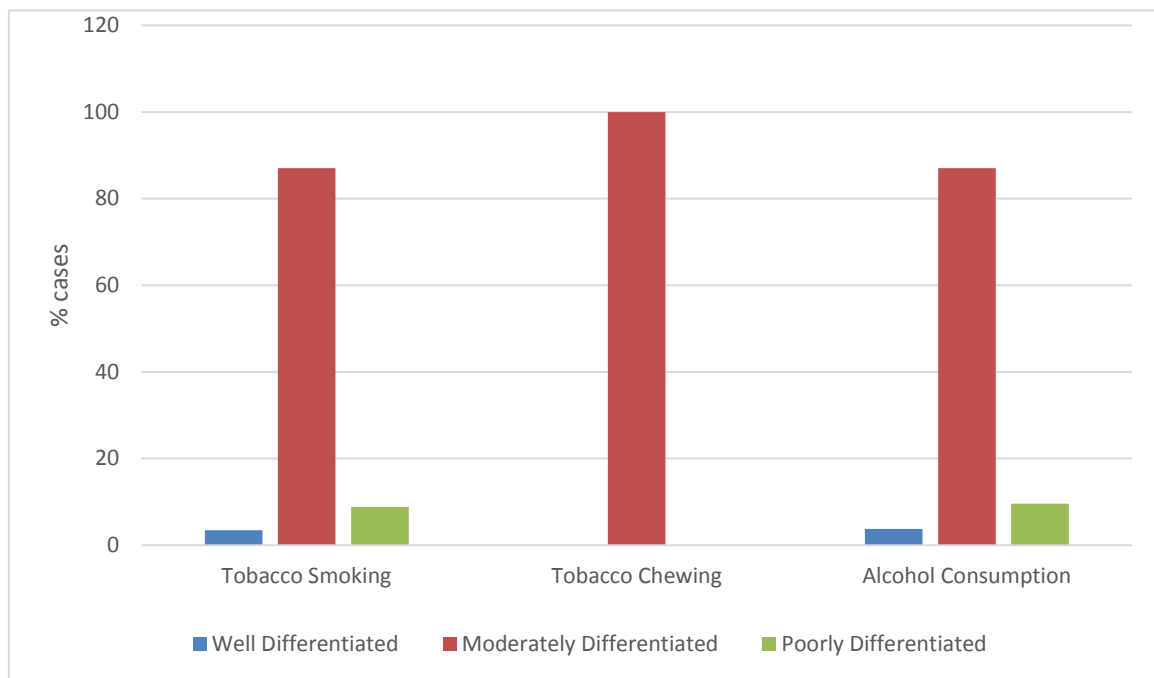


Figure 3.17 Degrees of differentiation versus risk factors.

CHAPTER FOUR:

Discussion

4.1 Trends

The total number of OSCC cases as reported by the Department of Oral Pathology, University of the Witwatersrand, over the ten year period 2004 to 2013, is 1049. This is a higher number than the 510 cases reported by Khammissa *et al* in their seven-year South African study (10). Although it is lower than the 1919 cases by Muller *et al* in the United States of America (USA), the study spanned a period of 35 years (116). The total number of OSCC cases reviewed in our study, fluctuated annually over the ten year period; however, on average, the number of cases diagnosed in 2013 ($n = 87$) is lower than those diagnosed in 2004 ($n = 167$). This decreasing trend may be attributed to a rising awareness of the condition by both patients and clinicians, which has led to early diagnosis and intervention. Indulgence in high-risk habits is on a decrease as campaigns surrounding smoking cessation and HPV vaccination are becoming more popular.

Although the total number of OSCC cases has decreased, there is a statistically significant increase in the percentage of females that presented with OSCC from 2004 (22.1 %) to 2013 (37.9 %) ($p < 0.0001$). This increasing gender trend is comparable to that of international studies and has been attributed by several authors to the changing lifestyle factors among females, including an increased recent trend in smoking among females, alcohol consumption and infection with HPV (12,28–30,32–34). The percentage of female smokers in our study increased by 11 % over the ten year period; a result that is in keeping with Warnakulasuriya *et al* in 2009, Rikardsen *et al* in 2014 and Franceschi *et al* in 2000 who reported an increase in the number of female smokers as a result of changing lifestyles (2,16,31).

4.2 Gender

In our study, the total number of females is 28.4 % ($n = 1038$) and males is 71.6 % ($n = 1038$). This is a higher percentage of females than reported by Hille *et al* during the period 1988 to 1995 in South Africa (117). Our average male to female ratio is 2.5:1 which is lower than that found by Khammissa *et al* (2.92:1) during the period 1995 to 2002 (10). Our lower male to female ratio supports the percentage increase in females diagnosed with OSCC. However, Khammissa *et al* reported a statistically significant difference in the male to female

ratio of Blacks (3.74:1) and Whites (1.96:1) (10). Our gender ratio is higher than that of several studies from developing countries including Acharya *et al*, Al-Rawi *et al* and Pires *et al* in India, Iraq and Brazil respectively, who reported male to female ratios averaging 2:1 (20–22). In the developed country of Norway, a lower ratio of around 1:1 was reported by Rikardsen *et al* (16). Nigeria is considered to be a developing country, however Effiom *et al* in 2008 observed a low male to female ratio of 1.4:1 which is in line with findings made in developed countries (16,28). These lower ratios are in keeping with a global reported trend of decreasing differences in the prevalence of OSCC between the genders. Our higher ratio suggests that differences are decreasing in South Africa but not at as fast a rate as those reported where the male gender predilection has almost been eliminated (2,16,31). Our finding shows that males are still significantly more affected by OSCC than females. A study in Northeastern Hungary by Nemes *et al* in 2008 showed a marked OSCC predilection for males with a male to female ratio of 5.2:1 which is comparable to the male to female ratio found by Khammissa *et al* for Blacks (3.74:1) (10,23).

4.3 Age

In our study, the age distribution of OSCC in both males and females showed a progressively increasing trend, peaking in the 51 to 60 age group and then gradually decreasing until the 91 to 100 age group. A similar trend was seen by Muller *et al* in 2008, while Carvalho *et al* in 2005 reported an increasing trend until the age of 75 years (116,118). Our findings may suggest that risk factors were commenced at a similar age in both genders. The male to female ratio in the 51 to 60 age group was higher (2.8:1) than the overall male to female ratio (2.5:1). However, the highest male to female ratio was seen in the 41-50 age group (4.5:1). The male to female ratios of our study showed a reversal with increasing age; while females under 30 years showed a higher percentage of OSCC, males dominated over the 31 to 90 age group. In the final decade of 91 to 100, females again showed a higher percentage than males.

Our study found 57.3 years to be the mean age at diagnosis (mean age of males = 56.7 years; mean age of females = 58.7 years), which is younger than the findings of Rikardsen *et al* in Norway (66.3 years) and Pires *et al* in Brazil (62.3 years) (16,21). In contrast to our results, Effiom *et al* in Nigeria reported an even younger mean age of 45 years. Khammissa *et al* in South Africa reported on data from 1995 to 2002 and distributed their results based on the race of patients in their cohort. Blacks were diagnosed with OSCC at a younger mean age (57 years) than Whites (61 years), and the result for Blacks was consistent with the overall mean

age in our study (10). OSCC occurring at a younger age in South African patients when compared with those elsewhere, could be explained by the low socioeconomic status of the country as a whole, coupled with the immunosuppression and limited or delayed access to health care facilities.

Bodner *et al* found genetic sensitivity in young patients (18–39 years) who were diagnosed with tongue OSCC, with no known risk factors. They associated the development of OSCC in patients with systemic diseases or syndromes that predispose cancer development to genetic instability (95). In our study, 7.1 % (n = 72) of cases were 40 years or younger. Similarly, in a developed country, Rikardsen *et al* showed 7% under the age of 40 (16). Khammissa *et al* reported 9% to be 40 years or younger and Thailand and Brazilian studies reported 4.7% and 3% respectively (10,21,29). Nigerian studies by Effiom *et al* and Adeyemi *et al* found large numbers of young patients at 40% and 17% respectively (28,119). The reasons for our 7.3 % young cases may be related to genetic factors, systemic conditions, HIV-related immunosuppression or early onset of high-risk behaviour. The literature has demonstrated that the occurrence of OSCC in children and adolescents is extremely rare (90). Our results concur with this finding as only 0.005 % (n = 5) of our cases were patients under the age of 20 years (two cases in the 1-10 age group and three cases in the 11 to 20 age group). Of these, two had been previously diagnosed with XP, a 2-year-old female and a 12-year-old female. The 2-year-old presented with OSCC of the upper and lower lips while the 12-year-old presented with OSCC of the lower lip only. In keeping with this finding previous studies reported the lip and tip of the tongue to be the most common sites of involvement in XP-associated OSCC (95,120,121). Coulombe *et al* presented a primary XP-associated OSCC on an uncommon site, the gingiva, in an 8-year-old female from Zimbabwe (122). Of our five cases of albinism, three presented at the age of 22 years with OSCCs of the lower lip. The lips are common sites for albinism-associated OSCC as described by Chidzonga *et al* (87). Persons with XP under the age of 20 years and Black sub-Saharan persons with albinism are associated with a 1000 fold increased risk of developing cutaneous SCC. Although the risk of developing SCC of the lip and tip of the tongue is increased in the former due to UV light exposure, the prevalence of OSCC in these patients has not been well described (123,124).

From our study, an 11-year-old, HIV-positive female was reported with multiple foci of OSCC involving the gingiva, buccal mucosa and hard palate; she had no other reported risk factors. In the literature, Butt *et al* in 2012 reported an HIV-positive, 17-year-old female who presented with OSCC involving the buccal mucosa (51). However, synchronous OSCC in

HIV-positive children has not been well described in literature and may provide an opportunity for further research in this area.

4.4 Race

Our study could not comment appropriately on the race of our cohort due to the 94.4 % (n = 991) of reports that did not specify the patients' race. In contrast, studies that perused the South African National Cancer Registry as a source of data provided comprehensive results based on the race of patients that present with OSCC in South Africa (109,110,117). In the most recent National Cancer Registry of 2011, Black males were reported with the highest percentage of mouth cancers at 1.92% while Asian females were the highest at 1.21% (19). Khammissa *et al* found that OSCC was diagnosed at a younger age in Blacks than Whites and the proportion of Black males in the Black population group was greater than that of White males in the White population group (10). Ayo-Yusuf *et al* found that among Asian/Indian South Africans, oral and pharyngeal (OAP) cancer incidence was higher among females than males and OAP cancer was highest among Coloureds and lowest among Blacks. They found that OAP cancer incidence increased significantly among Coloured South Africans over the period under review (6).

4.5 Risk factors

Tobacco smoking is the most common risk factor in this study (66.0 %, n = 208), and is associated with OSCC involving the floor of mouth (37 %, n = 77) (p = 0.0064), lower lip (6.3 %, n = 13) (p = 0.015), retromolar area (12.5 %, n = 26) (p = 0.015) and upper lip (0 %, n = 0) (p = 0,078). Alcohol consumption was reported in 17.1 % of cases (n = 54) and was most significantly associated with lesions on the lower lip (1.9 %, n = 1)(p = 0.010). Concurrent use of tobacco and alcohol was found in 17.1 % (n = 54) of our cases. Our results are shared by several studies around the world, and due to their global popularity, Warnakulasuriya *et al* has categorised tobacco smoking and alcohol consumption to be two of the most well-established risk factors for the development of OSCC (64). It has also been reported that when used together, tobacco and alcohol are strongly synergistic (21,22,64,125–128). In Eastern countries, however, the high incidence of OSCC is attributed to the chewing of betel quid and areca nut (16,73,74). Only one case of tobacco chewing was found in our study (0.3 %, n = 1) and therefore cannot be considered representative of this population. However, awareness of the habit as a risk factor should be established as South Africa is home to many Asian migrants who may present with an areca nut chewing habit and subsequent OSCC

development. Although we found tobacco smoking and alcohol consumption to be more prevalent in males, there were no statistically significant associations found between gender and known risk factors. The prevalence of OSCC at the lower lip was statistically significantly higher in non-users of alcohol (13.3 %) when compared to users of alcohol (1.9 %) ($p = 0.010$).

HIV-positive results accounted for 7.6 % ($n = 24$) of our cases. Within which, 62.5 % ($n = 15$) were male and the age range peaked between 31 years and 60 years. The lower lip (25 %, $n = 6$) and hard palate (25 %, $n = 6$) were most affected in HIV-positive individuals although both sites are considered rare for the development of OSCC in HIV-negative cases. Similarly, the dorsal surface of the tongue is considered to be exceedingly rare for OSCC in HIV-negative individuals, and has been described in the past as a myth or misdiagnosis (129). It is, therefore, interesting, that the dorsal surface of the tongue was affected in 16.7 % ($n = 4$) of our cases in the HIV-positive group. Similar to those of HIV-negative cases, 87.5 % ($n = 21$) of OSCCs were moderately-differentiated in this group. This finding is in contrast to the reported tendency for poor-differentiation in HIV-positive patients (51). Butt *et al* from Kenya in 2012 showed similar results, in that OSCC presented in younger HIV-positive patients however, their HIV-positive cases presented on the tongue and floor of the mouth most commonly (51). The number of cases under the age of 40 years has not significantly increased in the ten year period involved in our study. This steady trend could suggest that immunosuppression secondary to HIV infection has not had as great an impact on the incidence of OSCC. This may be due to South Africa's efficient antiretroviral (ARV) treatment roll out programme which managed to increase access to HIV treatment by 75% between 2009 and 2011 (130).

Albinism showed a 2.2 % ($n = 7$) prevalence in our study, followed by sun exposure (1 %, $n = 3$), oral snuff use (1 %, $n = 3$) and XP (0.6 %, $n = 2$). Although these risk factors are established on their own in the development of OSCC, the prevalence of all of them in one cohort has not been sufficiently documented in the literature (2,83–87). Other diseases and conditions reported by this study include diabetes (23.1 %, $n = 3$), hypertension (30.8 %, $n = 4$), hepatitis C (7.7 %, $n = 1$), tuberculosis (30.8 %, $n = 4$) and mental retardation (7.7 %, $n = 1$). These conditions have not been described in the literature as having a role in OSCC development.

4.6 Site of involvement

Several cases were characterised by multiple sites of involvement, and therefore, our “n” value for sites exceeds our total number of reports. The most common site of OSCC involvement in this study was the lateral border of the tongue (20.1 %, n = 333) followed by the floor of the mouth (18.5 %, n = 306). Of all the cases of SCC of the lateral border of the tongue, 37 % (n = 77) were associated with smoking and 40.7 % (n = 22) with alcohol consumption. OSCC on the floor of mouth was associated with smoking in 37 % (n = 77) of the cases and alcohol consumption in 35.2 % (n = 19). Observations from the literature show that tobacco smoking and alcohol consumption predispose to OSCC of the tongue and floor of mouth due to the pooling of tobacco smoke and alcohol at these sites (16,21,70,78,79). Similarly, Rikardsen *et al* found the mobile tongue and Khammissa *et al* reported the tongue as the most common site of involvement (10,16,21). Our findings were different from those of Asian studies which show a higher incidence of OSCC in the buccal mucosa and gingiva than in the tongue. This site predilection is linked to the placement of the areca nut in the buccal sulcus which renders this site more susceptible to OSCC development (8,20,29). Two Brazilian studies showed differing results; Pires *et al* found the border of the tongue to be most commonly affected while Marocchio *et al* found the gingiva to be most affected (21,131). We concur with Khammissa *et al* and Pieteresma *et al* in that the lower lip (12.7 %, n = 133) was more affected than the upper lip (2.3 %, n = 24) in this study (10,80). Rikardsen *et al* and Jainkittivong *et al* did not differentiate between upper and lower lips and Sharma *et al* reported on the labial mucosa in general (8,16,29). However, in our study, upper lip lesions were statistically more significantly associated with females (5.1 %, n = 15) than males (1.2 %, n = 9) ($p = 0.0007$). Similarly, Pietersma *et al* in the Netherlands showed the majority of their upper lip cases to occur in females (58 %) as compared to males (41.3 %) (80). They suggested that females may have a genetic predisposition to upper lip OSCCs, furthermore, they documented that during sun bathing, females are positioned with the upper lip more inclined towards the sun, and thus, increasing the risk of upper lip OSCCs (80). The retromolar area was found by our study to be more prevalent in males than in females with a 3.9:1 male to female ratio.

4.7 History of previous cancer

In our study, 3.5 % (n = 37) of reports alluded to an unspecified history of previous cancer, however it was not clear whether the current OSCC represented a recurrence, a second primary tumour or a metastasis. The remaining 96.5 % may have represented one of two

possibilities: the absence of a previous history or the failure to indicate the history of a previous cancer by the clinician on the request form.

4.8 Metastasis

Metastasis was specified in 1.4 % (n = 15) of our cases however no distinction was made between regional and distant metastasis. Lymph node metastasis is reported in approximately 40% of all OSCCs (96). Our low rate of metastatic spread may be an indication of underreporting and difficulty in determining metastasis based on a clinical examination alone. The site most commonly associated with metastasis was the floor of the mouth, exclusively (n = 4) or in association with the lateral, ventral and dorsal surfaces of the tongue (n = 2). Male cases accounted for 73 % (n = 11) of the metastases.

4.9 Histological differentiation

Moderately-differentiated OSCCs accounted for 82.3 % (n = 835) of our cases, while well-differentiated and poorly-differentiated cases were at 3.2 % (n = 32) and 14.6 % (n = 148) respectively. Our finding is comparable to that of Khammissa *et al* who observed 80 % moderately-differentiated OSCCs and 6 % of well-differentiated OSCCs in their study. They reported a significantly higher frequency of well-differentiated OSCCs in Whites than Blacks, and the reverse was true for poorly-differentiated OSCCs (10). Abroad, Fang *et al* reported well-, moderately-, and poorly-differentiated oral squamous cell carcinomas in 36 %, 56 %, and 8 % of patients, respectively (132). Our finding of a higher percentage of poorly-differentiated than well-differentiated OSCC is in contrast with other studies (29). This may be due to the delay in seeking medical assistance, with subsequent advanced stage at the time of diagnosis of OSCCs in South Africa. Well-differentiated OSCCs were most common on the lower lip, with a 2.4:1 male to female ratio. While moderately- and poorly-differentiated OSCCs both showed a preference for the lateral border of the tongue, the degree of differentiation were not significantly affected by risk factors.

CHAPTER FIVE:

Conclusion

5.1 Limitations

This study utilised data in the form of histopathological reports and slides retrieved from the archives in the Department of Oral Pathology, University of the Witwatersrand. Histopathological reports are heavily reliant on microscopic examination request forms for clinical and demographic data which are not consistently and completely provided by clinicians.

5.2 Summary and conclusion

The biggest strength of this study is the large sample size of 1049 cases of OSCC diagnosed in a single centre. The overall incidence of OSCC over the period 2004 to 2013 showed a downward trend, despite the increased incidence of OSCC in females from 22.1 % in 2004 to 37.9 % in 2013. This variation could be attributed to the overall cessation of high-risk habits as awareness surrounding OSCC increases. The increased trend in the incidence of OSCC in females could be attributed to the 11 % increase in female smokers seen over the ten-year-period of the study. Our male to female ratio suggests that differences between the genders are decreasing in South Africa but at a slower rate than those of reports from elsewhere. Tobacco smoking was the most common risk factor for the development of OSCC and was most associated with lesions of the floor of the mouth, lower lip, upper lip and retromolar areas. Alcohol (17.1 %, n = 54) was the second most common risk factor and was most associated with lesions of the lower lip. HIV was most commonly associated with OSCC of the lower lip and hard palate. XP and albinism were the most common risk factors in cases under the age of 25. There were no significant association between risk factors and gender. Although a rare site of involvement, OSCC of the upper lip was found to be statistically significant in females. Contrary to most studies, this study reports a higher percentage of poorly-differentiated OSCCs compared to well-differentiated OSCCs.

5.3 Recommendations

Within the limits of this study, we recommend a standardised approach when filling in microscopic examination request forms and compiling histopathological reports. Key factors to be considered in request forms when there is a high index of suspicion for OSCC include

the patient's age, gender, race, associated risk factors, medical history including immune status, a detailed history of previous cancer, site of involvement and the presence or absence of metastasis. In histopathological reports the degree of differentiation should be indicated particularly in cases where the Broder's grading system is emphasised over the invasive front grading system.

Further studies may be necessary to describe the prevalence of OSCC in XP and albinism particularly in persons younger than twenty years of age. However considering the rarity of these conditions a multicentre study may be necessary for this purpose.

The paucity of information characterising OSCCs in young HIV-positive individuals, provides an area for further research.

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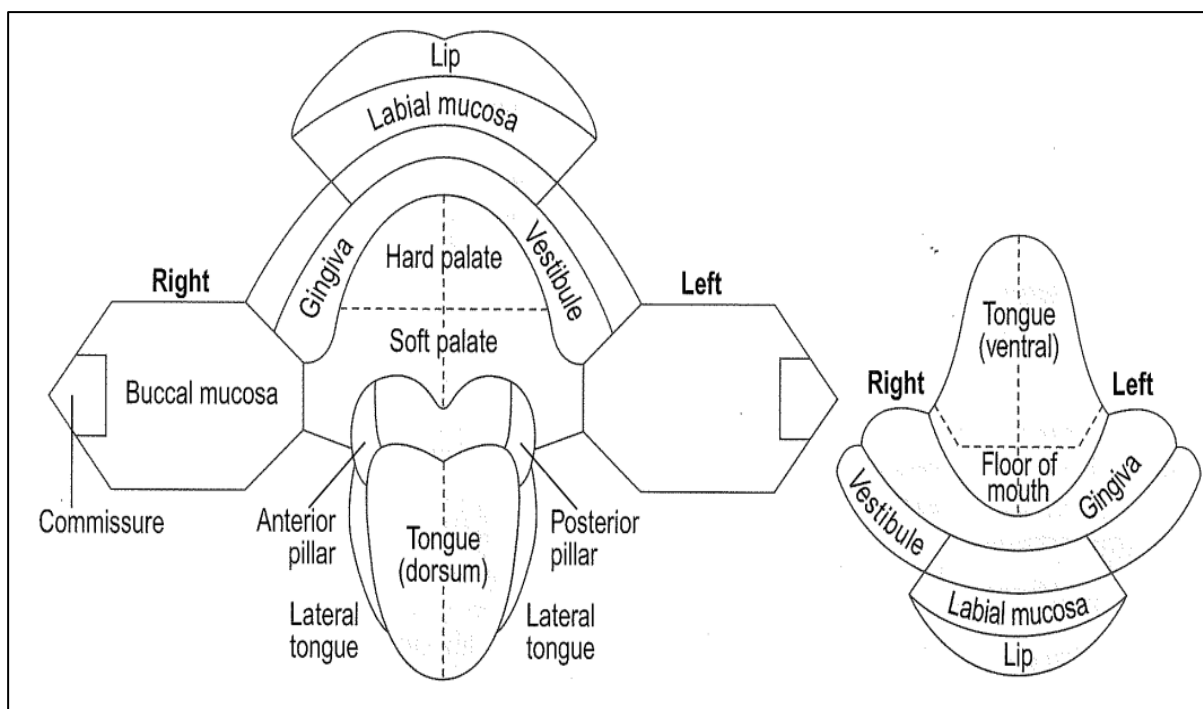
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The mouth chart described by Crispian Scully in Oral And Maxillofacial Medicine, The Basis Of Diagnosis And Treatment in 2008. (114)



APPENDIX B
Data collection sheet

Study identification number											
Year of report authorisation											
Age											
Gender	Male					Female					
Race	Black/African		White		Coloured		Indian/Asian			Other	
Risk factors	Tobacco smoking		Tobacco chewing		Alcohol consumption			Other			
History of previous cancer	Yes					No					
Site of involvement	Upper lip	Lower lip	Gingiva	Buccal mucosa	Hard palate	Floor of mouth	Tongue Dorsal Ventral lateral			Retro molar area	
Presence of metastasis	Yes					No					
Is the lesion keratinising?	Yes					No					
Histopathological degree of differentiation	Well-differentiated			Moderately-differentiated				Poorly-differentiated			
Other											

APPENDIX C
Approval of title



Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

06 June 2016
Person No: 303657
TAA

Dr T Mohangi
P O Box 2923
Brooklyn Square
0075
South Africa

Dear Dr Mohangi

Master of Science in Dentistry: Change of title of research

I am pleased to inform you that the following change in the title of your Research Report for the degree of **Master of Science in Dentistry** has been approved:

From:

To: **A comparative analysis of clinicopathological characteristics and trends of oral squamous cell carcinoma between men and women over a ten year period**

Yours sincerely

A handwritten signature in black ink, appearing to read 'Sandra Benn'.

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

APPENDIX D
Ethics clearance certificate



R14/49 Dr Tashta Mohangi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160676

NAME: Dr Tashta Mohangi
(Principal Investigator)
DEPARTMENT: Oral Medicine and Periodontology
Department of Oral Pathology, University of the Witwatersrand
PROJECT TITLE: A Comparative Analysis of Clinicopathological
Characteristics and Trends of Oral Squamous Cell
Carcinoma between Men and Women over a Ten Year
Period
DATE CONSIDERED: 24/06/2016
DECISION: Approved unconditionally
CONDITIONS:
SUPERVISOR: Prof Sindisiwe Shangase and Dr Sizakele Ngwenya
APPROVED BY: 
Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL: 27/06/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. I **agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in June and will therefore be due in the month of June each year.

Principal Investigator Signature _____

Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX E
Turn-it-in report

% 5	% 5	% 5	% 2
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet Source	% 2
2	file.scirp.org Internet Source	% 1
3	cgp.iarjournals.org Internet Source	% 1
4	F M A Butt. "Oral squamous cell carcinoma in human immunodeficiency virus positive patients: clinicopathological audit", The Journal of Laryngology & Otology, 12/14/2011 Publication	% 1
5	Submitted to University of Witwatersrand Student Paper	% 1