Title: Epidemiology of Oral Malignancies in the Sudan

(2004-2008)

Esraa Mosalleum

A mini-thesis submitted to the Faculty of Dentistry, University of the Western Cape, Cape Town, South Africa, in partial fulfilment of the requirements for the degree of Magister Chirurgiae Dentium in Oral Pathology.

Supervisor: Prof J.J. Hille

Co-supervisor: Prof A. Suleiman

01-02-2014

DECLARATION

I Esraa Mosalleum hereby declare that *Epidemiology of Oral Malignancy in Sudan (2004-2008)* is my own work, that has not been submitted before for any degree or examination at any university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

_____

Signature of the candidate

14 November 2014

Cape Town

DEDICATION

I dedicate this work to my parents, my brothers and sisters, my supportive husband and my lovely child Mohamed for all their support, encouragement, patience and sacrifice to enable me to pursue my studies.

ACKNOWLEDGEMENTS

I am grateful to my mentor and supervisor Prof J.J. Hille for his guidance and assistance throughout the course of my study.

Special thanks Prof A. Suleiman my co-supervisor for his advice and valuable comments.

I would also like to thank the staff of Khartoum Dental Teaching Hospital for providing the data for the study.

Epidemiology of Oral Malignancy in Sudan

(2004-2008)

KEY WORDS

Age Standardised Incidence Rates

Epidemiology

GLOBOCAN

Oral cancer

Sudan

ABSTRACT

Background: Reports on the global incidence of oral neoplasms indicate reduced data from Africa. Population based studies of oral cancer in Sudan and other regions of Africa are scarce. Oral cancer in Sudan constitutes a serious health problem, and squamous cell carcinoma (SCC) is the most prevalent type of oral malignancy. There are descriptive epidemiologic studies from Sudan that have reported high a frequency rate of oral cancer in Sudanese males, linking this high incidence to Toombak, a product of oral snuff mixed with sodium bicarbonate (Idris *et al*, 1995(b)), but to date no population-based studies of oral cancer incidence in Sudan have been performed or published.

Title: Epidemiology of Oral Malignancy in Sudan (2004-2008).

Aims and Objectives: The objectives of the study were to analyse the pattern of distribution and to determine the minimum age standardized incidence rates (ASIR) and the cumulative (lifetime) risk (CR) of oral & lip squamous cell carcinoma / oral malignancy by site, age and gender for the 5-year period 2004 -2008.

Methods: The records of patients with oral & maxillofacial and salivary malignancies (OMFS) referred to Khartoum Dental Teaching Hospital (KDTH) and the population census data were accessioned. Data was captured using Microsoft Excel 2007® and the ASIRs for oral squamous cell carcinoma (OSCC) were calculated using the direct International Agency for Research on Cancer (IARC) method. These results were compared with the on-line global cancer statistics database (GLOBOCAN - WHO/IARC) for 2008 and 2012. Records of oral cancer cases during the period of the study were obtained from KDTH. The information

included in the raw data collected were the file number for patient identification, year of diagnosis, age, sex, site of the lesion, histological diagnosis, the International Classification of Diseases-10 (ICD10) codes, the referring unit and the state from which the patient was referred. The population data for the years of the study and the five age group stratifications was obtained from the Central Statistical Office in Khartoum, Sudan. The data was analysed using Microsoft Excel, 2007®. Age standardized incidence rate of oral & lip squamous cell carcinoma/ oral malignancy was calculated using the direct IARC method.

Results: Of the total Sudanese population of 36.3 million in 2006, 649 OMFS malignancies (M : F=1.44:1) were captured at KDTH during the 5-year period; 390 (M : F=1.67:1) were (intra) oral squamous cancers (OSCC) and verrucous carcinomas (VC). The ASIR for OSCC/VC in Sudan was calculated as 3.19 for males and 1.83 for females (M : F=1.74:1), however the pooled ASIR in the Khartoum and Gezira States was 30% higher for males (4.21) and 14% higher for females (2.09, M: F=2.01:1). The incidence over the 5 years of separately recorded lip SCC/VC in Sudanese males was 26 and 8 for females (M : F=3.25:1). The ASIRs of combined oral & lip SCC/VC in Sudanese males was 3.45 and 1.88 for females (M : F=1.84:1). These compare relatively well with the GLOBOCAN data which estimates a slightly lower ASIR of 3.3 for males and somewhat higher ASIR of 2.1 for females (M : F=1.57:1). The cumulative (lifetime) risk (CR 0-74) of developing oral and lip cancer was 1: 182 for males compared to 1: 831 for females. For oral cancer (excluding lip), the CR was almost similar for males (1: 181); while females showed a markedly higher CR (1: 344).

Conclusion: The combined ASIRs of oral & lip SCC/VC from the Khartoum and Gezira states differed from the ASIRs calculated for the entire Sudan and from the GLOBOCAN estimates. The recording of cancer incidence data can vary according to the (incorrect) labelling of anatomical locations and diagnosis. The numbers are influenced by geo-political, environmental and socio-economic factors, and referral bias.

TABLE OF CONTENTS

DECLARATION 2

DEDICATION 3

ACKNOWLEDGEMENTS 4

KEY WORDS 5

ABSTRACT 6

TABLE OF CONTENTS 9

LIST OF TABLES 13

LIST OF FIGURES 14

CHAPTER 1 14

1. INTRODUCTION 17

CHAPTER 2 20

2. LITERATURE REVIEW 20

2.1 Introduction 20

2.2 Epidemiology 21

2.2.1 Global epidemiology 21

2.2.2 Epidemiology of head and neck cancer in Africa 23

2.2.3 Oral cancer in Sudan 25

2.2.4 Age, gender and site prevalence 27

2.3 Risk factors 28

2.3.1 Established and possible risk factors 28

2.3.2 Toombak 29

2.3.3 HPV and Head and Neck Cancer 31

2.3.4 Molecular carcinogenesis of oral cancer 32

CHAPTER 3 34

3. AIMS AND OBJECTIVES 34

3.1 Aim 34

3.2 Objectives 34

3.3 Hypothesis 34

CHAPTER 4 35

4. STUDY DESIGN AND METHODOLOGY 35

4.1 Study design 35

4.2 Study population and sampling 35

4.3 Inclusion criteria 35

4.4 Exclusion criteria 36

4.5 Data capturing 36

4.6 Data analysis 36

4.7 Definition of terms and formula used in calculation of age ASIR..... 37

4.8 Ethical considerations..... 40

CHAPTER 5 41

5. RESULTS 41

5.1 Age distribution..... 45

5.2 Site distribution 47

5.3 Geographical distribution and referral of cases 49

5.4 Incidence rates 50

5.4.1 Age specific rates..... 50

5.4.2 Age adjusted incidence rates 55

5.5. 95% Confidence intervals 57

5.6. Cumulative risk and cumulative rate 61

CHAPTER 6 62

6. DISCUSSION..... 62

6.1 Age distribution..... 63

6.2 Anatomic sites..... 64

6.3 Incidence rates 66

6.4 Cumulative risk (0-74) 71

CHAPTER 7 72

7. CONCLUSION AND RECOMMENDATIONS 72

CHAPTER 8 74

8. LIMITATION OF THE STUDY 74

APPENDICES 75

Appendix 1: Ethics clearance certificate 75

Appendix 2: ICD-10 Nomenclature of oral cavity topography 76

Appendix 3: An abstract from the raw data recorded in KDTH..... 81

Appendix 4: Numbers of cases of intraoral squamous cell carcinoma, excluding lip cancer per age group per year for females 81

Appendix 5: Numbers of cases of lip squamous cell carcinoma, per age group per year for males 88

Appendix 6: Numbers of cases of lip squamous cell carcinoma, per age group per year for females 90

Appendix 7: Cumulative rate (%) of oral cancer for Sudanese males and females 92

Appendix 8: Cumulative risk (%) of oral cancer for male and female residents in Khartoum and Gezira 92

REFERENCES…….93

LIST OF TABLES

Table 1.Total number of reported cases of intraoral, lip, major salivary glands and maxillary sinus malignancies recorded per year: 42

Table 2. Distribution of the total cases reported in the period of the study for males and females 42

Table 3: Age adjusted incidence rate per 100 000/ year for oral cancer in males and females 56

Table 4: Age adjusted incidence rate per 100 000/ year for oral cancer in males and females in Khartoum and Gezira states 57

Table 5: Depicts the cumulative risk (0-74) of developing oral cancer for Sudanese males and females 61

Table 6: Depicts the cumulative risk (0-74) of developing oral / oral & lip SCC in Khartoum and Gezira (combined), for males and females 61

Table 7: Comparison of the estimated ASIR from GLOBOCAN and KDTH: 68

LIST OF FIGURES

Figure 1: The Republic of Sudan 19

Figure 2. Bar graph depicting the frequency of distribution of all malignancies for the 5 years..... 43

Figure 3. Bar graph depicting the pattern of all oral maxillofacial malignancies reported during the 5 year period of the study..... 43

Figure 4. Bar graph depicting the site distribution of the total oral and maxillofacial malignancies reported during the study period..... 44

Figure 5: The age distribution for Sudanese males and females for the year 2006 45

Figure 6. The age of distribution of all malignancy cases reported during the study period..... 46

Figure 7. Age distribution of intraoral malignancy for males for the five years 46

Figure 8. Age distribution of intraoral malignancy for females for the five years 47

Figure 9. Site distribution of oral & lip malignancies reported during the 5 year study period for males and females 48

Figure 10. Bar graph depicting site distribution of maxillary sinus, salivary glands and bone malignancies by gender and male to female ratio 48

Figure 11. Depicts the geographical distribution of the reported cases in KDTH over the 5 years. 49

Figure 12: Depicts the referral process of all the cases presented at KDTH..... 50

Figure 13: Line graph with trend showing age specific morbidity rate per 100 000 per year for OSCC in males..... 51

Figure 14: Line graph with trend showing age specific morbidity rate per 100 000 per year for OSCC in females..... 51

Figure 15: Line graph with trend showing age specific morbidity rate per 100 000 per year for oral & lip SCC in males..... 52

Figure 16: Line graph with trend showing age specific morbidity rate per 100 000 per year for oral & lip SCC in females..... 52

Figure 17: Age specific incidence rate with trend for OSCC for males in Khartoum and Gezira states 53

Figure 18: Age specific incidence rate with trend for OSCC for females in Khartoum and Gezira states 54

Figure 19: Age specific incidence rate with trend for oral & lip SCC for males in Khartoum and Gezira states..... 54

Figure 20: Age specific incidence rate with trend for oral & lip SCC for females in Khartoum and Gezira states..... 55

Figure 21: Depicts the ASIR per 100 000 of OSCC/VC for males and females in the Sudanese population..... 58

Figure 22: Depicts the ASIR per 100 000 of oral & lip SCC/VC for males and females in the Sudanese population 58

Figure 23: Depicts the ASIR per 100 000 of OSCC/VC for males and females in the Khartoum and Gezira states 59

Figure 24: Depicts the ASIR per 100 000 of oral & lip SCC/VC for males and females in the Khartoum and Gezira states 59

Figure 25: Depicts ASIR per 100 000 of all oral malignancies and 95% for Sudanese males and females 60

CHAPTER 1

1. INTRODUCTION

Oral cancer is an increasing health problem world-wide. However, its distribution varies widely in different populations. The epidemiology of cancer is influenced by the geographical environments, variation in age, sex, and site, climates and associated risk factors.

Globally oral cancers combined with pharyngeal cancer are the sixth most prevalent cancers in males the world and follows lung cancer, stomach, breast, colon/ rectum and cervix/ corpus uteri cancer. The estimated annual incidence for oral cancer was around 275,000 with the majority of these cancers occurring in the developing countries (Warnakulasuriya, 2009).

Unfortunately, comprehensive population-based studies of oral cancer in Sudan and other African regions show limited numbers. The available statistics from descriptive studies showed that the incidence of oral cancer in Sudan is higher among males compared to females (Idris *et al*, 1998; Idris *et al*, 1995(a, b); Idris *et al*, 1992). The lack of reliable data has emphasised the need for Sudan to develop means of data gathering in order to address the cancer scourge. An updated analysis of oral cancer distribution in the Sudan is nevertheless needed.

The most common risk factor associated with oral cancer in Sudan is Toombak, a form of smokeless tobacco with high carcinogenic potential due to high contents of tobacco-specific nitrosamines. Toombak has been extensively investigated in previous studies and conflicting results regarding the carcinogenic potential of this product and

its potential relationship with oral cancer have been reported (Idris *et al*, 1991; 1992; 1995(a); 1996, 1998).

The purpose of this study was to analyse the pattern of distribution and the incidence rates of oral cancer for patients who attended the Khartoum Dental Teaching Hospital (KDTH) during the five years of the study. It was felt that a descriptive analysis of oral cancer data archived at this main referral hospital for oral cancer in the country could aid in assessing the extent of the problem. Furthermore, this study could also facilitate categorising the population in risk groups, thereby helping to assign resources for higher risk population groups. The research is also aimed at establishing a series of future studies on the oral cancer incidence in Sudan to enable comparison with global data and possibly tracking future changes in the local trends of oral and oropharyngeal cancer.

Figure 1: The Republic of Sudan

CHAPTER 2

2. LITERATURE REVIEW

2.1 *Introduction:*

The literature revealed a great lack of consistency in defining the term oral cancer. The anatomy of the oral cavity is very complex. The oral cavity proper consists of different sites e.g. tongue, palate, gum, floor of mouth, retro-molar area and the lip. Malignancies arising in the oral cavity are complicated by the presence of different origin tissue types such as oral mucosa, salivary glands, jaw bones, lymphoid tissue and supporting structures. This is further influenced by the presence of the skin covering the lips and the area of the vermilion border which is believed by many researchers to include a cohort of skin-associated tumours in fair-skinned individuals. This variability in the term oral cancer complicates the interpretation of the epidemiological data of oral cancer (Tapia and Goldberg, 2011).

Oral and pharyngeal cancers grouped together are ranked as the sixth most common cancers in the world. Ninety percent of upper aero-digestive tract malignancies are squamous cell carcinomas (SCC). Data of oral cancer from Africa is scarce and global incidence studies of oral neoplasms showed reduced data from Africa (Warnakulasuriya, 2009).

2.2 *Epidemiology:*

2.2.1 Global epidemiology

Oral cancer is a global health problem which has a profound effect on the general health and the quality of life. Several studies have reported varying results on the global incidence and trend of oral and oropharyngeal cancer. However, in the past decade head and neck cancer was considered to be a heterogeneous disease. This was ascribed to the emergence of the subtypes of Human PapillomaVirus (HPV) - associated head and neck squamous cell carcinoma (HNSCC) and molecular demonstration of the heterogeneity of head and neck squamous cell carcinoma using advanced molecular techniques. This change in the biology and risk factor association in HNSCC is reflected in the change in the clinical and the biological characteristics of head and neck cancer (Leemans *et al*, 2011).

According to the global statistics, the incidence of head and neck cancer showed great variation in the different geographical areas. In South and South East Asia, high incidence rates of oral cancer excluding lip cancer have been reported, followed by parts of Western and Eastern Europe, the Caribbean and parts of Latin America and the Pacific region. Carcinoma of the oral cavity is the most common cancer in men in countries with increased risk factors such as India, Bangladesh, Sri Lanka, and Pakistan, accounting for 25% of new cancer cases per year (Warnakulasuriya, 2009).

In the past twenty years, the age standardized incidence of oral cancer showed a steady increase in some parts of Europe. This rise in the trend of oral cancer in those countries has been attributed to increased use of tobacco and alcohol consumption (Warnakulasuriya, 2009). According to the European Union 2004 report,

oropharyngeal cancer is the 7th most prevalent cancer. France and Hungary reported the highest incidence within the European Union. The lifetime risk of developing oropharyngeal cancer in the European Union was estimated as 0.37% for females and 1.85% for males (Black *et al*, 1997; Warnakulasuriya, 2009). In the United Kingdom (UK), oral and pharyngeal cancers accounted for 1.6% of all cancer cases reported in 2003, making UK one of the European countries with the least reported cases of oral and pharyngeal cancer. However, recent studies have shown that the disease is on the increase in young adults in the UK. Most of UK cancer registries record 6% of the total oral cancer cases in young adults less than 45 years of age (Conway *et al* 2006). Robinson and Macfarlane (2003) reported an increase in oropharyngeal cancer in males (31%) and (16%) for females during 1989-1996 in Scotland. The changes involved principally males aged 34-65 years despite the stable mortality rate (Robinson and Macfarlane, 2003).

The United States of America (USA) reported a declining trend of oral and pharyngeal cancer by 1.5% for all races (Warnakulasuriya, 2009).

In Hungary the incidence and mortality of oropharyngeal cancer have doubled in recent decades. Other countries in central Europe, e.g. Slovenia and Slovakia, have also reported increasing rates of oral cancer (Banoczy and Squier, 2004).

In a retrospective population based study in Nova Scotia for the period of 1983-1997, oral cancer accounted for 2% of all cancers. Lip cancer was the most prevalent site followed by the tongue. Fifty-three percent of oropharyngeal and lip cancers occurred above the age of 65 years. There was a dramatic increase in intraoral cancer in females and a lower increase in males (Howell *et al*, 2003).

The most frequently reported types of cancers in male Indians were cancers of the oral and pharyngeal sites, followed by oesophageal, lung, and laryngeal and stomach cancers. In the same manner, Singapore male Indians reportedly endure an increased rate of oropharyngeal cancers followed by lung and stomach cancers, but prostatic and colorectal cancers replaced oesophageal and laryngeal cancers in the most common five malignancies reported (Rastogi *et al*, 2008). More than 100,000 cases of oral cancer are registered per year in India. Some districts in India have the highest world incidence of tongue and mouth cancer; 6.1 per 100 000 and 7.1 per 100 000 respectively (Curado *et al*, 2007).

In Jordan a descriptive epidemiological study on malignant oral tumours (1991-2001) concluded that in north Jordanians, squamous cell carcinoma was the most common oral malignant tumour accounting for more than 84% of all oral malignancies. Other histological types included were: sarcomas 5.6%, adenocarcinomas 5.6%, and lymphomas 4%. Mouth NOS was the most common site affected (42.4%) followed by the lip (33%) and tongue (24%). In comparison with other international studies there was a low incidence of mouth and tongue cancer. Lip malignancies were the second most common tumours of the oral cavity in north Jordan while in global terms they showed lower incidence rates. Risk factors such as smoking, exposure to solar radiation and possible dietary factors have been recognized in the aetiology of oral cancer in Jordan (Rawashdeh and Matalka, 2004).

2.2.2 Epidemiology of head and neck cancer in Africa

There are only a few population based studies of oropharyngeal cancer from the African continent (Warnakulasuriya, 2009; Johnson, 1991). Curado *et al* (2007) described in “Cancer Incidence in Five Contents, Volume IX”, which indicate that the

only male populations in Africa that reported a mouth cancer rate of 1.0 per 100 000 per annum and above were those of Uganda, Kyadondo County (1.6 per 100 000), Egypt, Gharbiah (1.3 per 100 000), and Tunisia, Centre, Sousse (1.0 per 100 000). Only females in Egypt, Gharbiah and Uganda, Kyadondo County showed a rate of 1.0 per 100 000.

Hille *et al* (1996) reported oral cancer incidence rates of (all sites combined) in South Africa in 1988-1991. They did find a male preponderance in black, coloured and white groups, while females are affected more frequently in the Asian population. Lip cancer showed the highest age standardized incidence rate (ASIR) in white males. However, the trend of lip cancer showed a decline in the incidence rate compared to previous studies in their country. Altini and Kola (1985) reviewed oral SCC (OSCC) incidence rates in black subjects on the Witwatersrand, South Africa, for the period 1971-1980. They reported a tongue cancer incidence rate of 1.3 per 100 000 per year in black females.

Marimo and Hille (2006) concluded from a population-based study in Zimbabwe that oral malignancies comprise 1.8% of the total body malignancies. Lip cancer was three times more common in whites than blacks, and the most affected age group was the elderly. SCC and Kaposi sarcomas were the leading malignancies. There was an increased rate of Kaposi sarcoma among adults which was attributed to the HIV/AIDS epidemic in the region.

Another descriptive epidemiological study in a Zimbabwean population showed that squamous cell carcinoma was the most common malignancy, involving predominantly mandibular gingiva. SCC of the floor of the mouth and tongue were

found to be the second and the third sites involved. Lip cancer was uncommonly reported (Chidzonga and Mahomva, 2006).

Another study done on the East African population in Muhimbili Hospital in Tanzania and Mulago referral hospitals in Uganda concluded the following: In Tanzania, SCC was the most common type of malignancy (32.75%), followed by Burkitt's lymphoma (32.40%) and Kaposi sarcoma (15.14%). Only one case of malignant odontogenic neoplasm (malignant ameloblastoma) was reported. On the contrary, in Uganda, Kaposi sarcoma was the most common malignancy accounting for (37.78%), followed by Burkitt's lymphoma (30.12%) and then SCC (19.67%). Regarding the gender distribution, most of the cases occurred in males. The age distribution showed a great variability for the different neoplasms. The second and third decades were the most common age distribution for most of the neoplasms; the sixth decade was the most frequent age for squamous cell carcinoma. The peak age for Burkitt's lymphoma was below 10 years, while 56.4% of the dominant malignancies in the sixth decade upwards were Kaposi sarcoma. Most of the mandibular lesions were ameloblastomas and no gender specific incidence was reported (Kamulegeya and Kalyanyama, 2008).

2.2.3 Oral cancer in Sudan

Previous reports on oral cancer in Sudan revealed a relatively high frequency compared to the neighbouring countries (Idris *et al*, 1995(b)). The most common type of malignancy reported was SCC which accounted for (66.5%), followed by tumours of the salivary glands (14.7%), neoplasms of non-odontogenic & non-epithelial origin (9.6%) and odontogenic neoplasms (8.6%). The frequency showed a high level of oral cancer in men compared to women. The older age groups of both genders showed a relatively high frequency of squamous cell carcinoma. Northern Sudanese suffer from

a high rate of SCC while southern Sudanese endure a higher rate of odontogenic and salivary gland neoplasms (Idris *et al*, 1995(b)). However, no site specific distribution pattern for intraoral malignancy has been reported.

Osman *et al* (2010) analysed the stage of presentation of 261 cases of malignant tumours registered at Khartoum Dental Teaching Hospital. They observed that most of the patients attending the hospital at a very late stage (94% of patients) were stage IV tumours. They also revealed that 66.3% of the attendees had clinically involved regional lymph node involvement. The economic status of the patients indicated that about 36% were from low socio-economic groups and 51.6% were dependent on other members of the family.

Idris *et al* (1992) demonstrated the aetiological association between the use of Toombak and SCC. This was linked to the high level of tobacco-specific nitrosamines in Sudanese snuff (Toombak), which was present at high concentrations in the saliva of oral snuff Sudanese users (Idris *et al*, 1991; 1992). The authors suggested that the distribution pattern of oral cancer in Sudan was influenced by factors such as the distance, transportation difficulties, socio economic factors, lack of education, and other factors preventing patients from seeking medical care (El-bashir *et a*l, 1989; Idris *et al*, 1992).

According to Templeton *et al* (1972) and Davis *et al* (1985), the pattern of neoplasms reported in Africa was endogenous to some African regions and similar types of neoplasms were seen in the neighbouring countries. They attributed this pattern to local environment, dietary factors, microbial agents and/or climate that influences the aetiology of these tumours.

2.2.4 Age, gender and site prevalence

Oral cancer is a disease that is greatly affected by the age stratification of the population, with 98% of patients being over 40 years of age. It is considerably more common among male gender in most countries. In Britain, lip carcinoma was eight times more common in men compared to women. Intraoral cancer used to be several times more frequent in males than females but the overall male to female ratio was 3:2, and in South East England recent figures showed little difference between the genders. This change was thought to be due to the progressive decline in the incidence in men with a static rate in women (Cawson and Odell, 2008). On the other hand tongue cancer was the most prevalent cancer in the United States, with an estimated percentage of 40-50% of oral cancers. In Asians, the buccal mucosa was the most common site for intraoral cancer (Warnakulasuriya, 2009). This distribution pattern was suggested to be linked to the habit of betel quid chewing (Warnakulasuriya, 2009; Byakodi *et al*, 2012). In a recent study, the lower alveolus was the most common site of involvement with oral cancer in India (Byakodi, 2012).

An epidemiologic and clinical oral cancer study conducted in India reported that carcinoma of the palate was associated with smoking and alcohol consumption. On the other hand lower alveolar mucosa and buccal mucosa were associated with chewing tobacco (Byakodi et al, 2012). In the past decade, the change in the trend of head and neck cancer was thought to be due to the impact of lifestyle factors and Human Papilloma virus (HPV) paralleled with a shift in the age, with younger age groups being affected (Westra, 2009).

2.3 *Risk factors:*

2.3.1 Established and possible risk factors

The incidence of oral cancer is influenced by many factors such as nutritional, immunological, occupational and other habitual, genetic, infectious and socioeconomic risk factors (Curado *et al*, 2009). The epidemiology of head and neck cancer showed recent changes in the trend and the risk factors association. Tobacco-associated head and neck cancer appears to be decreasing in men and beginning to rise in women. Tobacco and alcohol have been considered to play a very important role in the aetiology of oral cancer (Curado *et al*, 2009). The association of tobacco smoking and oral cancer is dose dependant (Petti, 2009). Human PapillomaVirus (HPV) infection, as discussed later, was suggested to be a factor of good prognosis in squamous cell carcinoma of the oral cavity and oropharynx (Curado *et al*, 2009).

Petti (2009) discussed the risk factors associated with head and neck cancer in detail. According to Warnakulasuriya (2009) alcohol and all forms of tobacco, including smokeless forms and snuff dipping, are considered well established risk factors for oral cancer. The author also mentioned that sunlight and radiation are potential risk factors for lip cancer.

The most common forms of smoking found in western and developing countries were cigarettes, cigars, cheroots, tobacco in pipes or handmade cigarettes. The different types vary in their tar and nitrosamine content, the method of combustion, the additive materials and methods of curing. There is significant association between smoking habit and the prevalence of OSCC. Marijuana usage has been recently identified as an

independent risk factor in HPV associated HNSCC (Westra, 2009, Gillison *et al*, 2008).

Possible risk factors for oral cancer also include HPV, immunodeficiency and ethnicity. Furthermore, mouth washes, genetic factors and periodontal disease are speculative risk factors for oral cancer development (Warnakulasuriya, 2009).

The low levels of mouth cancer in females compared to males and the increased risk of oral cancer in post-menopausal women may suggest the involvement of hormonal factors in the aetiology of oral cancer. High blood glucose and estrogen deficiency were suggested to be risk factors in females (Suba *et al*, 2009).

Some studies linked chronic trauma of the oral mucosa to oral cancer, especially when other risk factors are present (Piemonte, 2010; Lockhart *et al*, 1998).

2.3.2 Toombak

This is the most popular form of smokeless tobacco found in Sudan. It is made locally from tobacco powder that contains a high level of nicotine called *Nicotiana Rustica* and sodium bicarbonate, with a 4:1 ratio. The alkalinity of sodium bicarbonate increases the absorption of the nicotine from the mucosal surfaces (Idris *et al*, 1998). The habit of snuff dipping in Sudan is confined almost exclusively to males, with a daily consumption rate of 10 to 20 dips (Idris *et al*, 1998). The elevated risk found when investigating intraoral cancer sites in direct contact with Toombak compared to those with little or no contact, confirms the hypothesis that direct contact with the tissues is an important factor in the carcinogenesis of Toombak (Idris *et al*, 1995(a)). The most substantial evidence of the association between SCC and the use of Toombak is evident in the study of 62 patients of squamous cell carcinoma, 81% of

whom had used Toombak and the site of carcinoma was the site where the quid was kept (El-bashir, *et al*, 1989). The oral application of snuff in rats induces malignant tumours of the palate, gingival and tongue (Johansson *et al*, 1989). Studies have established and quantified several carcinogens in snuff including N-nitrosamines, volatile aldehydes, polycyclic aromatic hydrocarbons (PAH) and polonium-210 (Petti, 2009; Hoffmann *et al*, 1987; Djordievic *et al*, 1993). The N-nitrosamines (volatile and non-volatile) have been reported to be the most abundant carcinogens. The tobacco-specific nitrosamines (TSNA) derived from nicotiana alkaloids contribute about 70-90% of the total N-nitrosamines. Among these TSN the N-nitrosonornicotine (NNN) and 4-(methyl nitrosamine)-1-(3-nitrosonicotine pyridyl)-1-butanone (NNK) are very strong carcinogenic factors in many species (Petti, 2009; Hecht and Hoffmann, 1989). The carcinogenic potential of tobacco chewing is well established and is dependent on the dose, while the carcinogenic potential of snuffing is less prominent with some evidence from human studies (Petti, 2009; IARC, 2006; Warnakulasuryia and Ralhan, 2007; Weitkunat, 2007). The presence of NNK metabolites in Toombak suggests that the TSNA could be responsible for neoplastic transformation in the oral mucosa of Sudanese Toombak users (Idris *et al*, 1991, 1992). An association between the longer duration of Toombak use and oral cancer has been suggested. However, inconsistent results were observed from previous results regarding the effect of Toombak on the oral mucosa (Idris *et al* 1996; Ahmed and Mahgoob, 2007).

A recent in-vitro study comparing the adverse effects of Sudanese Toombak and Swedish snuff on human oral cells concluded that Toombak has a higher potential to damage normal oral keratinocytes and normal oral fibroblasts than Swedish snuff. This effect was thought to be due to blockage of the G2/ M cell cycle and induction of apoptotic pathways. The study also found that higher cumulative adverse effects were

observed on the normal oral keratinocytes with the use of Toombak extracts when compared to Swedish snuff. On the contrary, less pronounced adverse effects were observed on dysplastic oral keratinocytes. Furthermore, it was suggested that the dysplastic oral keratinocytes were more prone to progress to malignant transformation by Toombak but not by Swedish snuff (Costea *et al,* 2010).

Osman *et al* (2010) reported in a two year study conducted in Khartoum Dental Teaching Hospital that 28.7% of the oral cancer subjects were Toombak users and 88% of those patients had SCC. Interestingly they also noted that 56% of the Toombak dippers showed overlapping lesions of the mouth compared to 31.7% in non-Toombak users.

2.3.3 HPV and Head and Neck Cancer

The Human Papilloma Virus (HPV) is a circular double stranded DNA virus. The role of the HPV in carcinogenesis has been extensively investigated, especially in cervical cancer (Rautava and Syrjänen, 2012; Zur Hausen, 2002). Data regarding the association of the HPV and oral cancer remains controversial (Pannone *et al*, 2011; Chaudhary *et al*, 2009). However epidemiological and molecular bases provide support that the virus plays an important role in oropharyngeal cancer. The viral subtypes associated with carcinogenesis are labelled high risk viruses. HPV16 in particular is linked to HNSCC (Pannone *et al*, 2011; Leemans *et al*, 2011).

HPV associated SCC usually affects younger individuals (<40 years) with a male predominance. The histomorphology of this neoplasm shows non-keratinizing basaloid features. HPV associated SCC responds to chemo-radiotherapy and targeted immuno-stimulatory therapy (Pannone *et al*, 2011; Westra, 2009). A significant high relative risk of head and neck squamous cell carcinoma, associated with high risk

HPV, was evident among alcohol users. This suggests a synergistic effect between alcohol and HPV in the causation of the neoplasm (Pannone *et al*, 2011). On the contrary no synergistic effect between tobacco and HPV status was found (Pannone *et al*, 2011; Smith *et al*, 2004).

Most researchers consider HPV-associated SCC as a distinct group of head and neck squamous cell carcinoma. This entity is considered to be associated with different aetio-pathological factors, histomorphology, different molecular characteristics as well as clinical characteristics and outcome, compared to conventional HPV negative HNSCC. HPV-associated HNSCC have a more favourable prognosis (Leemans *et al*, 2011; Pannone *et al*, 2011; Rautava and Syrjänen, 2012).

2.3.4 Molecular carcinogenesis of oral cancer:

Agrawal *et al* (2011) and Stransky *et al* (2011) have demonstrated recent advances in the molecular pathogenesis of head and neck cancer using whole-exome sequencing performed on 100 HNSCC by the two studies. The fundamental roles of different molecular pathways involving HNSCC have been supported by many studies. These include molecular pathways involved in cellular proliferation and tumour suppressor function e.g. P53/ Rb/ INK4/ ARF / CCND1. Other pathways involved in terminal differentiation of cells, for instance P63/ Notch axis, have also been reported in a subset of HNSCC cases including HPV+ squamous cell carcinomas (Talora et al, 2005). Pathways involved in cell survival, particularly EGFR and its downstream pathways such as Phosphatidylinositol-3 kinase (PIK3CA) and RAS are commonly activated in HNSCC. Epidermal Growth Factor Receptor (EGFR) pathways are considered to be the most important chemotherapeutic targets in HNSCC (Rothenberg and Ellisen, 2012; Sharafinski, *et al*, 2010). In addition, transforming growth factor β

pathways (TGF- β) and SMAD genes have also been linked to tumour initiation and metastasis (Rothenberg and Ellisen, 2012). A potential pathway is *FAT1* gene mutations (Stransky *et al* 2011). Other potential gene targets with unclear functional significance in the causation of HNSCC are MLL2, NSD1 (Stransky *et al* 2011) and SYNE1 (Agrawal *et al*, 2011 and Stransky *et al* 2011).

On the other hand, in HPV-associated SCC, the HPV early oncoproteins; E6 and E7 interact with a variety of cell cycle genes and proteins (Rautava and Syrjänen, 2012). In particular the cell cycle regulator (p53) is affected by the former and retinoblastoma (RB) is affected by the latter (Leemans *et al*, 2011; Rautava and Syrjänen, 2012). The role of E5 viral oncoprotein was also investigated by Maufort and co-workers in 2010 (Maufort *et al*, 2010). E5 was found to cause continuous proliferation and delays differentiation of the keratinocytes. These effects are mediated through the interaction of the E5 oncoprotein with the epidermal growth factor receptor (EGFR) signalling pathway and platelet derived growth factor receptor (PDGF). Furthermore E5 oncoprotein enhances cell proliferation through down-regulation of tumour suppressors; p21 and p27 (Rautava and Syrjänen, 2012).

CHAPTER 3

3. AIMS AND OBJECTIVES

3.1 *Aim*

The aim of the study was to determine the incidence and to analyze the pattern of distribution of oral malignancies in Sudan for cases referred to Khartoum Dental Teaching Hospital during the 5 –year period, 2004-2008.

3.2 *Objectives*

The objectives of the study were:

1- To determine the prevalence of oral, maxillary sinus and salivary gland malignancies by gender, site and age.

2- To determine the minimum age standardized incidence rates (ASIR) and age specific rates of oral cancer by site and gender.

3- To determine the cumulative (lifetime) risk (CR) to develop oral cancer for the population under the study.

4- To compare the incidence rates of oral cancer to the corresponding GLOBOCAN figures.

3.3 *Hypothesis*

The incidence of oral and lip squamous cell carcinoma in the Sudanese population reflects male predominance.

CHAPTER 4

4. STUDY DESIGN AND METHODOLOGY

4.1 *Study design*

This was a retrospective, descriptive and analytic epidemiological study based on the study of data recorded at Khartoum Dental Teaching Hospital (KDTH) for the 5-year period (January 2004 - December 2008).

4.2 *Study population and sampling*

The data included in this study was obtained from Khartoum Dental Teaching Hospital for all patients with oral cancer recorded in the period of the study between January 2004 and December 2008. These records were based exclusively on histological biopsy reports referred from the national and private laboratories and the Pathology Department of the University of Khartoum. To prevent duplication other hospitals were not included in the study since almost all of the oral cancer cases were referred to Khartoum Dental Teaching Hospital for management.

4.3 *Inclusion criteria*

Data of all Sudanese residents newly diagnosed with malignant tumours during the period of the study (2004-2008) were included. The cases were classified into squamous cell carcinoma (SCC)/verrucous carcinoma (VC) and non-squamous groups. Intraoral cancer sites are classified according to the ICD-10 codes (Appendix 2).

4.4 *Exclusion criteria*

Patients with laryngeal and pharyngeal cancers were not included in the study as those patients were referred to the ear nose and throat units (ENT) for management. Metastatic lesions to the oral cavity were excluded from calculations of ASIRs.

4.5 *Data capturing*

All the records of oral and maxillofacial cases referred to KDTH during the period of January 2004 to December 2008 were obtained in a Microsoft Excel spreadsheet. The information included in the raw data was the file number for patient identification, year of diagnosis, age, sex, site of the lesion, histological diagnosis, the international classification of diseases-10 (ICD10) code (appendix 2), the referring unit and the state from which the patient was referred.

The raw data included the following sites: lip, tongue, gum, palate, floor of mouth, mouth NOS, maxillary sinus, jaw bone and major salivary glands.

4.6 *Data analysis*

The anatomical sites used to calculate (ASIRs) were lip, tongue, gum, palate, floor of mouth and mouth NOS. The latter five sites were designated as oral. Cancer cases from these sites were classified based on the histological diagnosis into SCC/VC and non-SCC. These groups were further separated into males and females. Each gender category was divided into five year age groups from 0-4 to 75+. Only the groups marked SCC/VC in each site were used to measure the ASIR for SCC/VC. Calculation of all oral malignancy ASIRs included both SCC and non-SCC for oral sites collectively.

The population data and the estimated population size for each age group for males and females were obtained from the central statistical office, Khartoum, Sudan. The population statistics obtained also included state specific population data. The 2006 statistics were used to calculate the age specific morbidity rate, adjusted age specific incidence rate; also known as ASIR, cumulative (lifetime) risk (CR) for oral cancer. The direct method described by the International Agency for Cancer Research (IARC) (Curado *et al,* 2007) was used to calculate the incidence and the cumulative risk estimates: ASIRs per 100 000 and CRs (0-74) for oral SCC/VC, combined oral and lip SCC/VC, lip SCC/VC and the total oral malignancies for all Sudanese patients referred to KDTH. Male and female ASIRs were designed separately. Adjustment for unknown age was made according to IARC method.

Similarly, ASIRs for oral SCC/VC and combined oral & lip SCC/VC were calculated for Khartoum and Gezira states separately.

All the calculations were conducted using Microsoft Excel 2007®, no data packages or other statistical tests were needed for the analysis.

4.7 *Definition of terms and formula used in calculation of age standardized rates:*

Crude incidence rate: -

Is the rate at which new cases occur in a population during a specific period of time. This rate is expressed as the average number of cases occurring per 100 000 person each year or 100 000 persons per years.

Crude incidence rate =

$$\frac{\text{Number of new cancer cases observed in the period (2004-2008)}}{\text{Total population in the period (2004-2008)}}$$

The calculation of this rate includes those cancers that had missing information about population group, sex, age.

Age specific rate: -

The adjusted rate for a specific age group. It is expressed as the rate of cases occurring in a specific age group per 100 000 persons.

Age standardized (adjusted) rate (ASIR):-

A weighed average of age specific cancer Incidence or mortality rates, in which the weights are the proportions of persons in the corresponding age group of a standard population. Using this rate permits comparison across populations with dissimilar age distribution.

$$\text{Age-standardised rate} = \sum_i \frac{d_i w_i}{y_i}$$

Such that *i* represent each age group

di: the number of cases in the ith age group

y_i: the population size in the ith age group

w_i: the weight applied for the ith age group

d_i/y_i being the age specific rate for each ith category

With the sum of the w_i being equal to 100 000 to express the ASIR per 100 000 Persons-years.

The standard worldwide population described by Segi (1960) and modified by Doll *et al*. (1966) was used for these calculations (Curado *et al*, 2007).

Adjustment for age unknown

Adjustment has to be made for the proportion of people in the age unknown category. The formula is: ASR x (total cases / cases with known age).

Calculation of variance of ASIR:

The first step for calculation of standard error is to calculate the variances for each age-specific expected number of cases based on the world standard population, cases with un-known age are included.

The second step is to sum all the age-specific variances. The variance for the age-adjusted rate for cancer of the oral cavity (World standard population) is then determined as sum of all variances/100 000*100 000

$$Var(ASR) = \frac{\sum_{i=1}^{18}\left(\frac{d_i * (y_i - d_i) * w_i^2}{y_i^3}\right)}{\left(\sum_{i=1}^{18} w_i\right)^2}$$

$$CI = \pm 1.96 * \sqrt{Var(ASR)}$$

Cumulative rate and cumulative risk: -

The cumulative cancer incidence rate can be used to calculate the cumulative life time risk (LR), that is, the probability of developing a cancer in one's lifetime. The following formula was used:

$$\text{Cumulative rate between 0 - 74 years old} = 5 \times \sum_{i=1}^{15} \frac{d_i}{y_i}$$

Such that *i*=5 year age group

di: the number of cases in the ith age group

y_i: the population size in the ith age group

4.8 *Ethical considerations:*

- The research proposal was submitted to the Faculty of dentistry, University of the Western Cape research committee for approval of the study.
- Permission was obtained from KDTH to get patients records for this study.
- Patient's confidentiality was strictly preserved with no names, addresses or contact details being divulged.

CHAPTER 5

5. RESULTS

During the five year study period (2004-2008), 649 cases of maxillofacial malignancies were registered in Khartoum Dental Teaching Hospital (KDTH). These included, intraoral and lip cancer, maxillary sinus and major salivary gland malignancies. Out of the total number of reported cases (458), 71 % were intraoral neoplasms (Table 2). The average male: female ratio for intraoral neoplasms was 3: 2. The average annual number of reported intraoral cancer cases was 92 cases, with 72 cases per year for males and 50 cases for females. There was a gradual annual increase in the total number of reported cases as depicted in Table 1 and Figure 1. The least number of cases were reported in 2004 (86 cases), and the highest number of cases were reported in 2008 (162 cases). Cases diagnosed as squamous cell carcinoma (SCC) constituted 72% of the total malignancies reported and 81% of intraoral malignancies. 4% of the registered cases were verrucous carcinomas (VC); 6% were sarcomas; and 4% were lymphomas (Figure 2). Lip cancer constituted 5.3% (35 cases) of the total number of the cases reported. Salivary gland tumours were the second most prevalent malignancies, constituting 13% of the total malignancies reported, of which major salivary glands contributed 5% (Figure 2). Cases diagnosed as VC showed a striking predilection for males with a 3.25: 1, male to female ratio.

Table 1.Total number of reported cases of intraoral, lip, major salivary glands and maxillary sinus malignancies recorded per year:

	2004	2005	2006	2007	2008	(2004-2008)
Males	50	64	92	96	94	396
Females	36	42	62	45	68	253
Total	86	106	154	141	162	649

Table 2. Distribution of the total cases reported in the period of the study for males and females

Total number of cancer cases reported (2004-2008)	F	M	Total
Bone	14	16	30
Major salivary gland	14	16	30
Maxillary sinus	17	40	57
Intraoral cancer	183	275	458
lip cancer	9	26	35
Others	16	23	39
Total	253	396	649

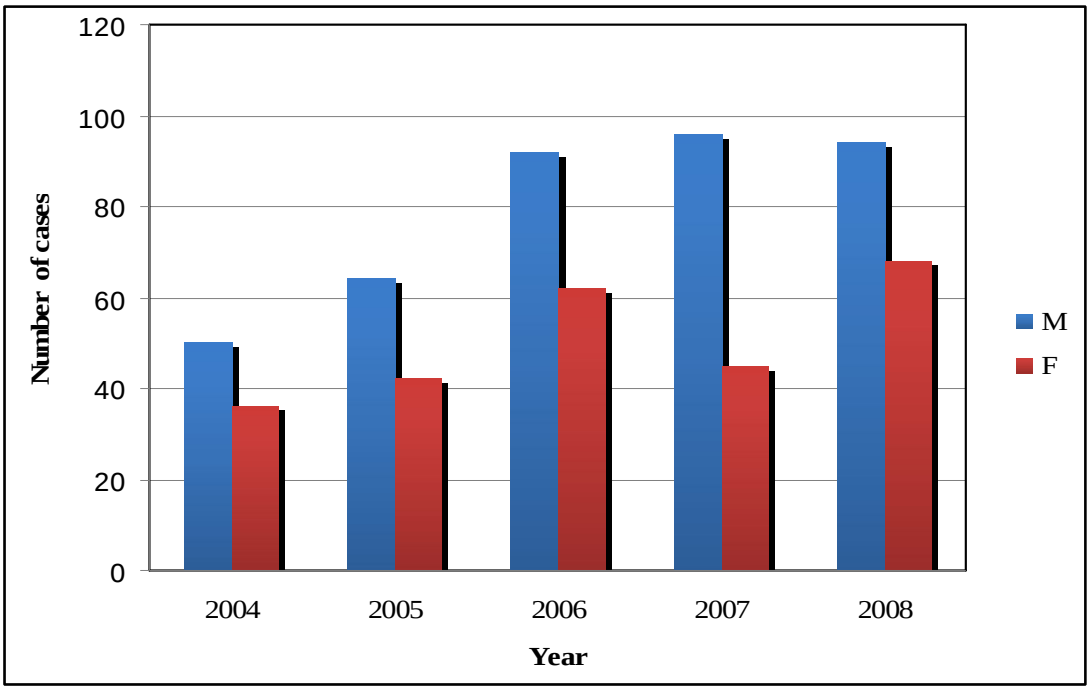

Figure 2. Bar graph depicting the frequency of distribution of all malignancies for the 5 years

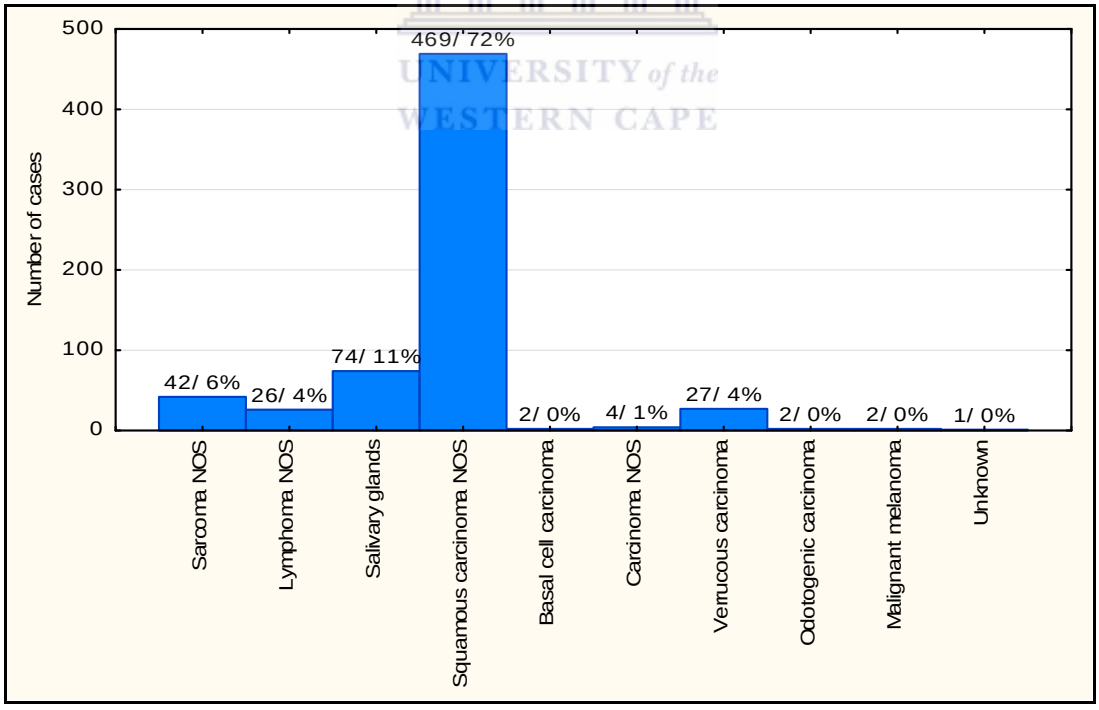

Figure 3. Bar graph depicting the pattern of all oral maxillofacial malignancies reported during the 5 year period of the study

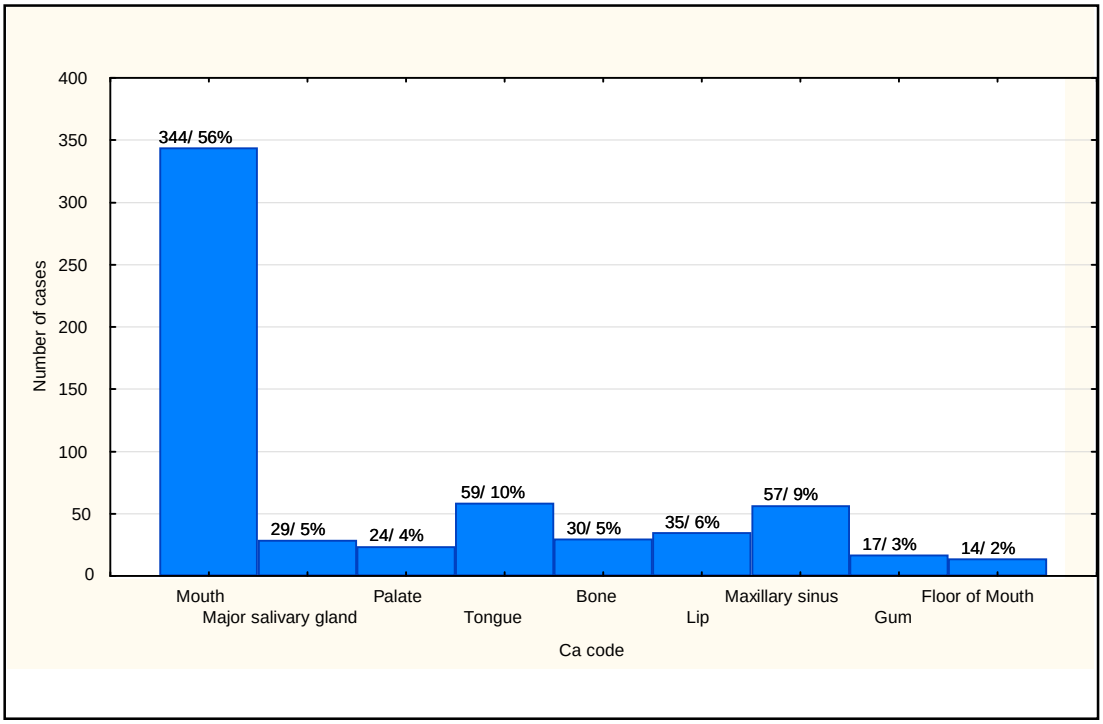

Figure 4. Bar graph depicting the site distribution of the total oral and maxillofacial malignancies reported during the study period

5.1 *Age distribution:*

The study population was estimated as 26.3 million in the mid-year of the study (2006). The distribution of the population follows the normal pattern with a broad base and a narrow top (Figure 5). There is a slight increase in the number of males compared to females but the ratio is almost consistent throughout the 5 year age distribution.

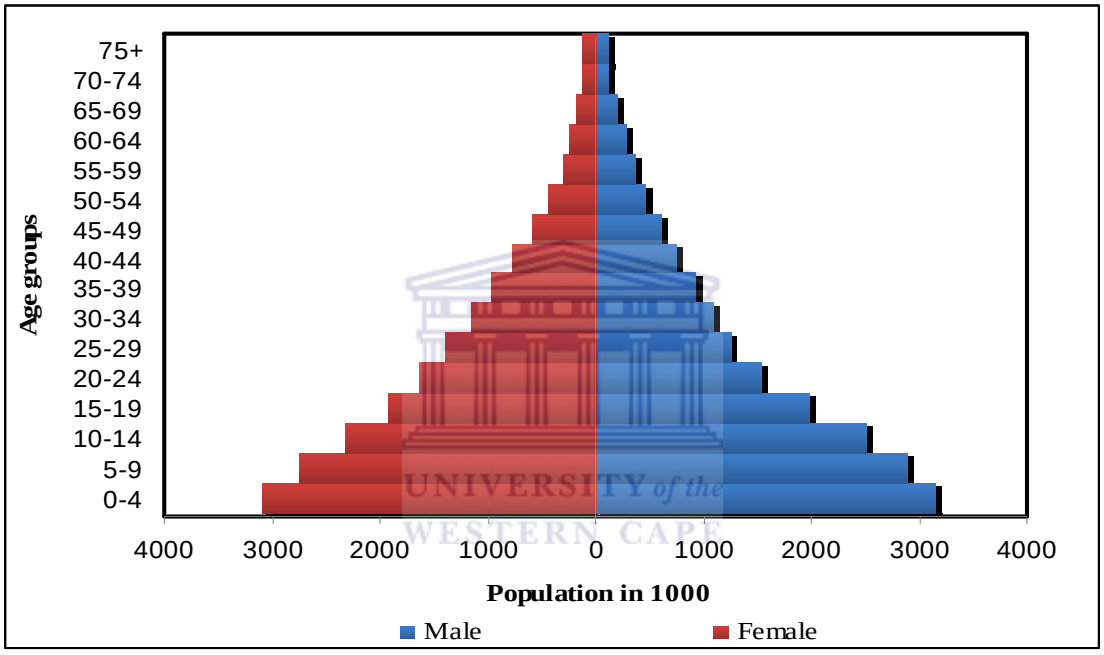

Figure 5: The age distribution for Sudanese males and females for the year 2006

In the population under study the highest number of reported cases was observed above the age of 75 years. However, there was a sharp increase in the number of reported cases at the age of 40-44 years, with a gradual increase in the number of reported cases thereafter (Figure 6). The prevalence of OSCC above the age of 50 years was 79% and 76% for males and females respectively (Figures 7 and 8).

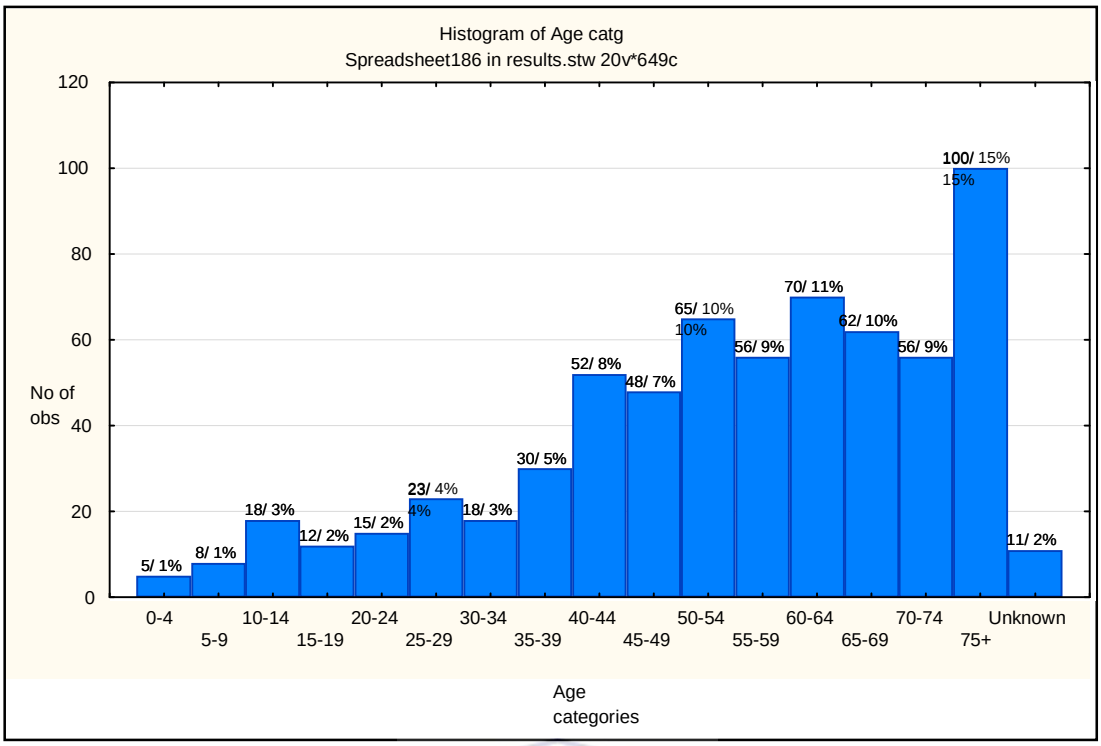

Figure 6. The age of distribution of all malignancy cases reported during the study period

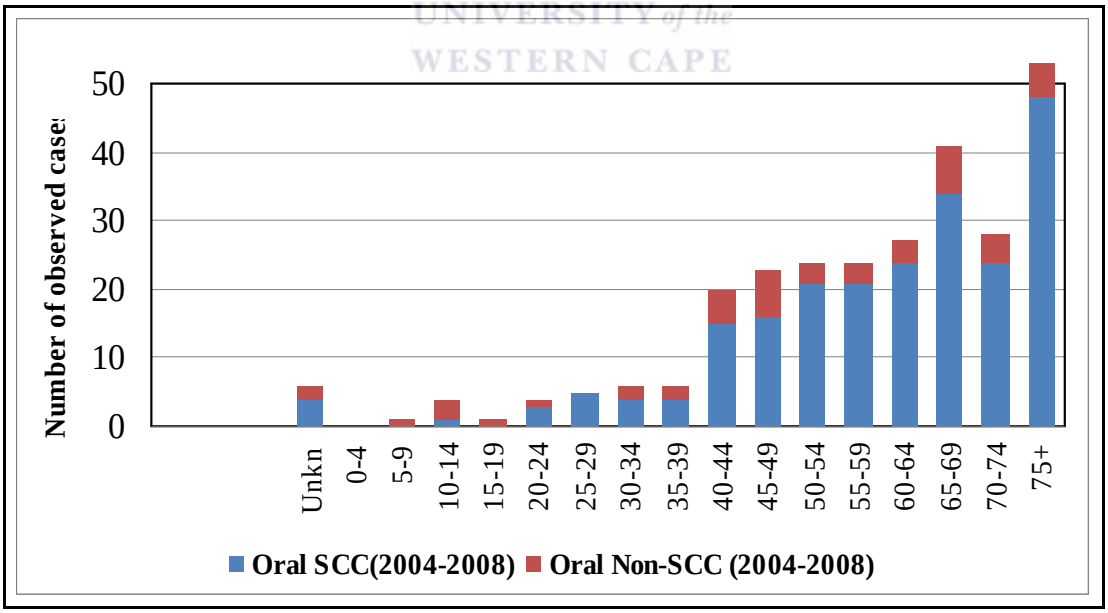

Figure 7. Age distribution of intraoral malignancy for males for the five years

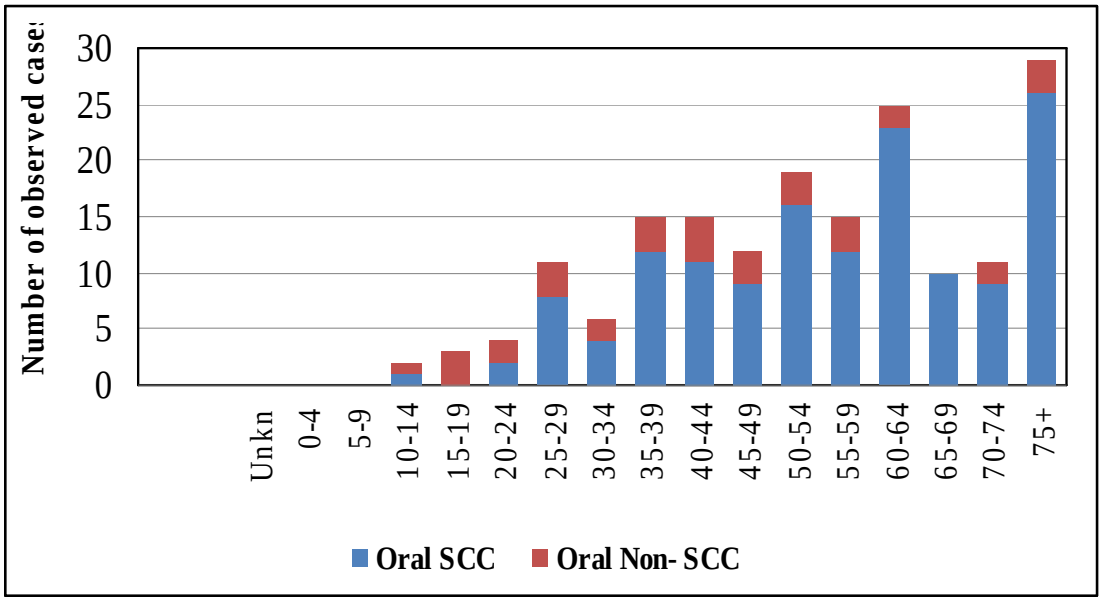

Figure 8. Age distribution of intraoral malignancy for females for the five years

5.2 *Site distribution*

During the 5 year study period, an average of 69.77% (344 cases) of the total oral malignancies involved more than one anatomic site. This constituted 72.4% in males and 65.6% in females (M: F= 1.1: 1). The tongue was the second most common site of neoplastic involvement (10%; 59 cases), followed by the lip (6%; 35 cases) (Figures 9 and 4). Tongue malignancies approximately showed equal distribution between males and females. However, intraoral malignancies involving more than one anatomic site had a male predilection with male-to-female ratio of 1.7:1, while lip cancer showed a higher prevalence in males; male-to-female ratio was 2.89: 1.

Maxillary sinus malignancies showed a male predilection with a 2: 1 ratio for males, while malignancies of salivary glands showed equal gender distribution (Figure 10).

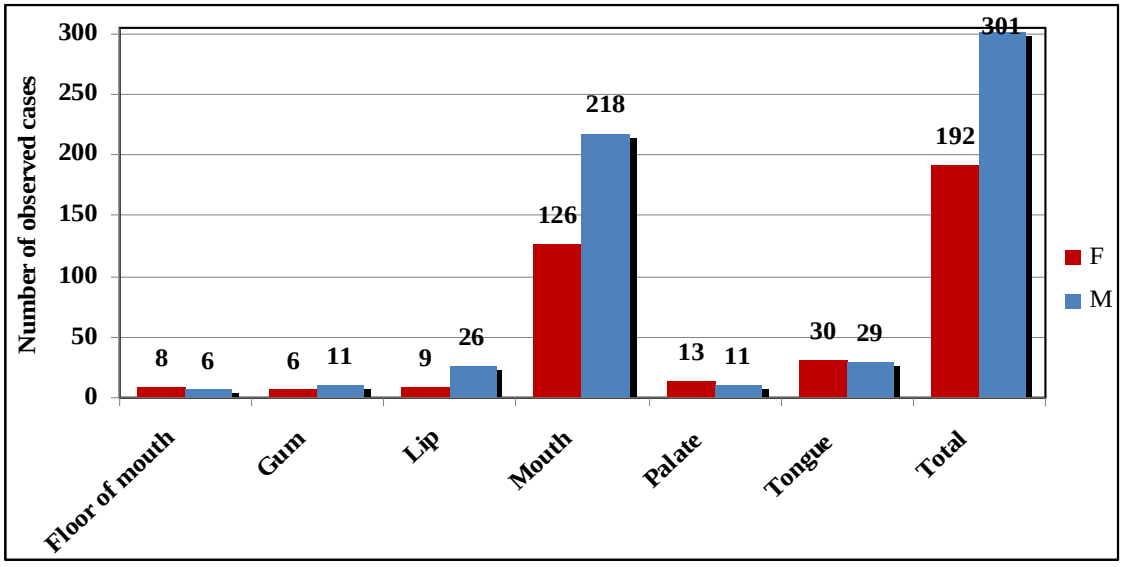

Figure 9. Site distribution of oral & lip malignancies reported during the 5 year study period for males and females

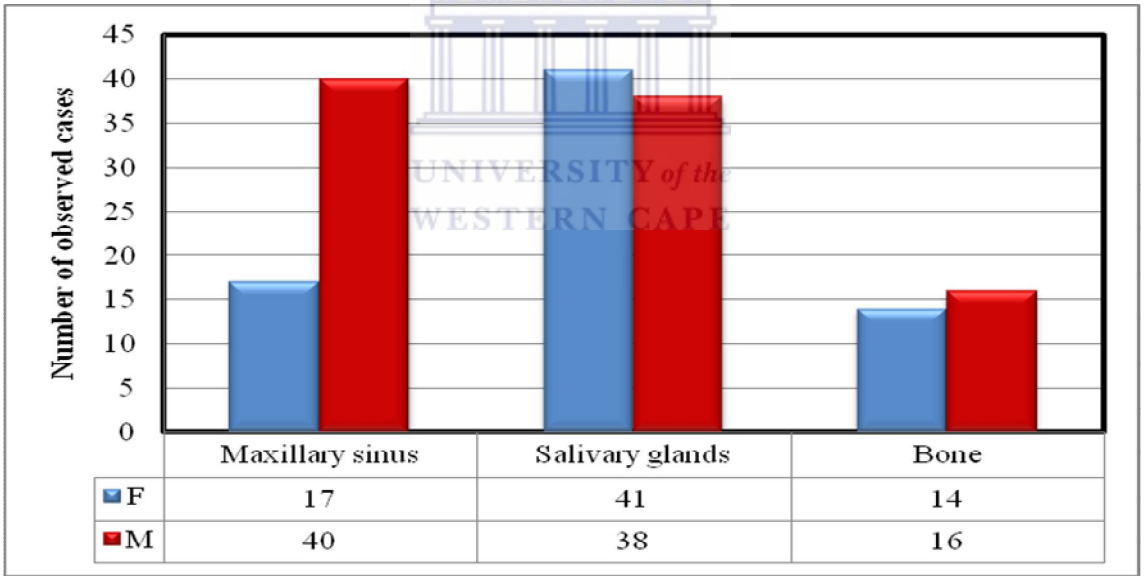

Figure 10. Bar graph depicting site distribution of maxillary sinus, salivary glands and bone malignancies by gender and male to female ratio

5.3 *Geographical distribution and referral of cases*

The geographical distribution of the cases reported during the five year study period is shown in figure 12. 28% of the cases reported were from Khartoum state. While cases from the eastern and the northern states collectively contributed to 21% each of the total cases. 15% of the reported cases were from Gezira state only. Less cases have been reported from the western and southern states collectively (Figure 11).

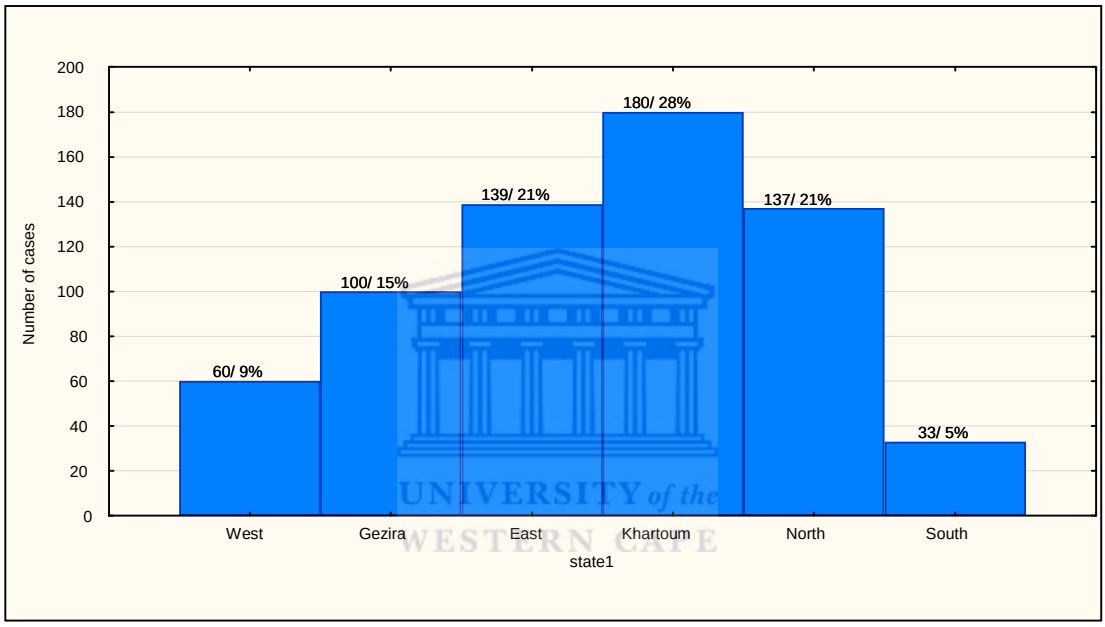

Figure 11. Depicts the geographical distribution of the reported cases in KDTH over the 5 years.

The majority of the cases (303 cases, 47%) were not referred. 37% of cases were referred from other govermental hospitals. The major referring units included Ear Nose and Throat units (ENT), Dermatology, Internal Medicine and Surgery. A few cases were also referred from Neurosurgery, Physiotherapy, Radiotherapy and Paediatrics (Figure 12).

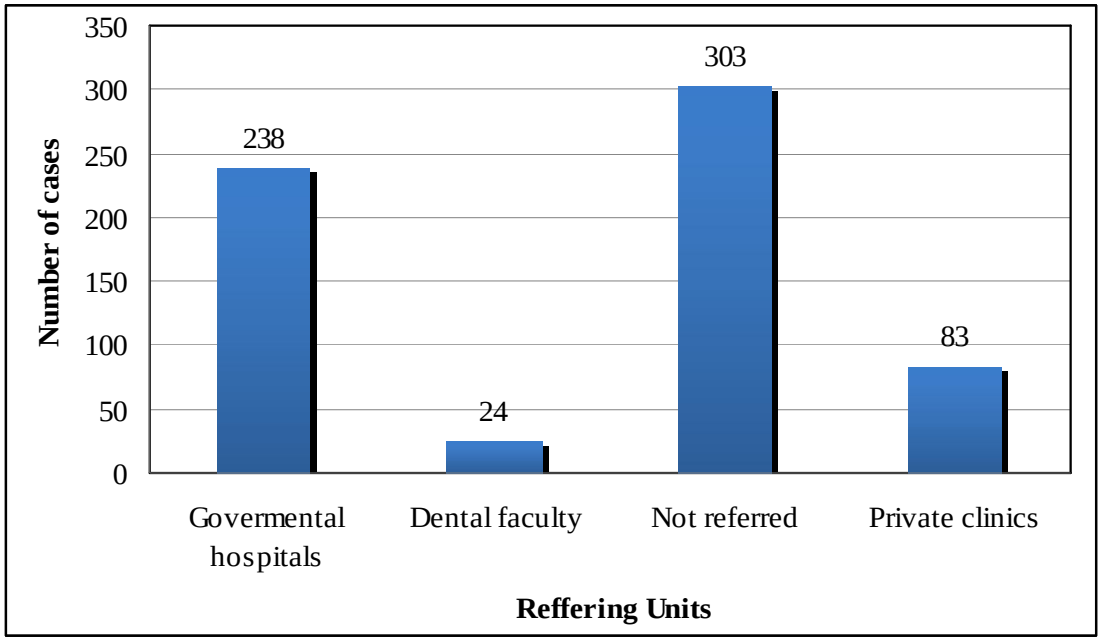

Figure 12: Depicts the referral process of all the cases presented at KDTH

5.4 *Incidence rates*

5.4.1 Age specific rates

All states combined:

The specific morbidity rate for (OSCC), including (VC) ranged from 0.00 to 46.58 per 100 000 per year for males and 0.00 to 22.75 per 100 000 for females. That peak age specific rate was observed at the age of 75+ for both genders (Figures 13 & 14). In females a smaller peak was also noted at 60-69 years; this peak was less noticeable in males. The age specific morbidity rate started increasing gradually at 35-39 years in females, while in males the increase was noted at the age of 40-44 years.

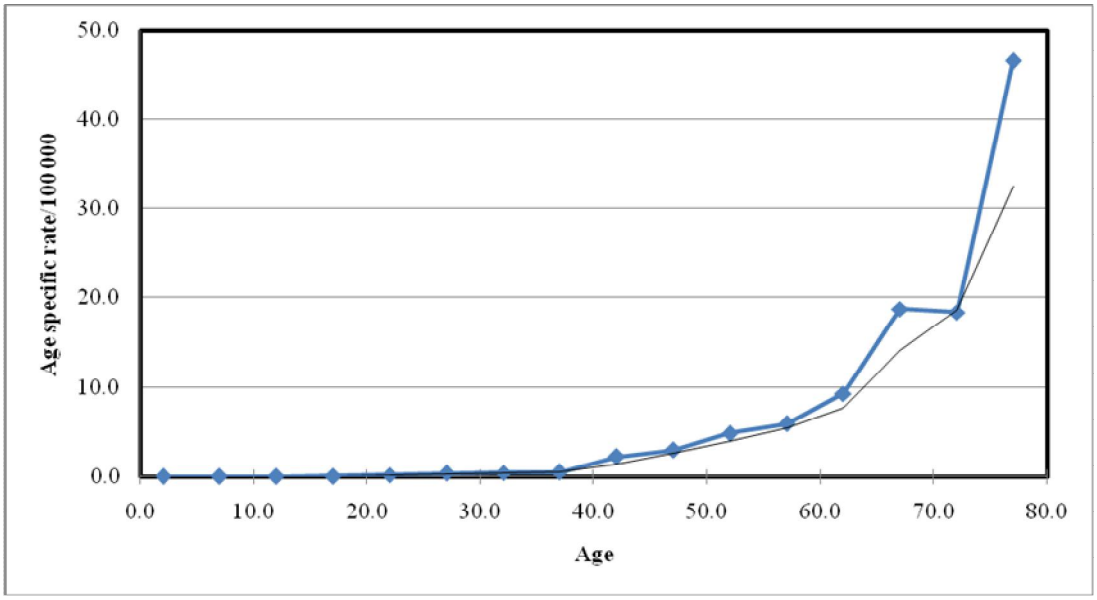

Figure 13: Line graph with trend showing age specific morbidity rate per 100 000 per year for OSCC in males

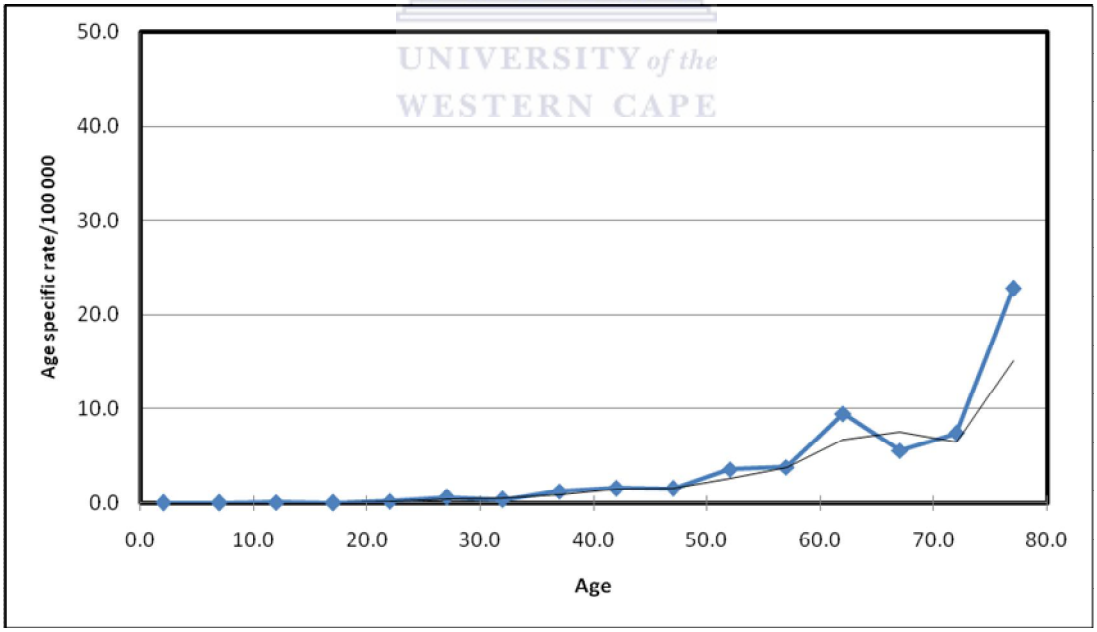

Figure 14: Line graph with trend showing age specific morbidity rate per 100 000 per year for OSCC in females

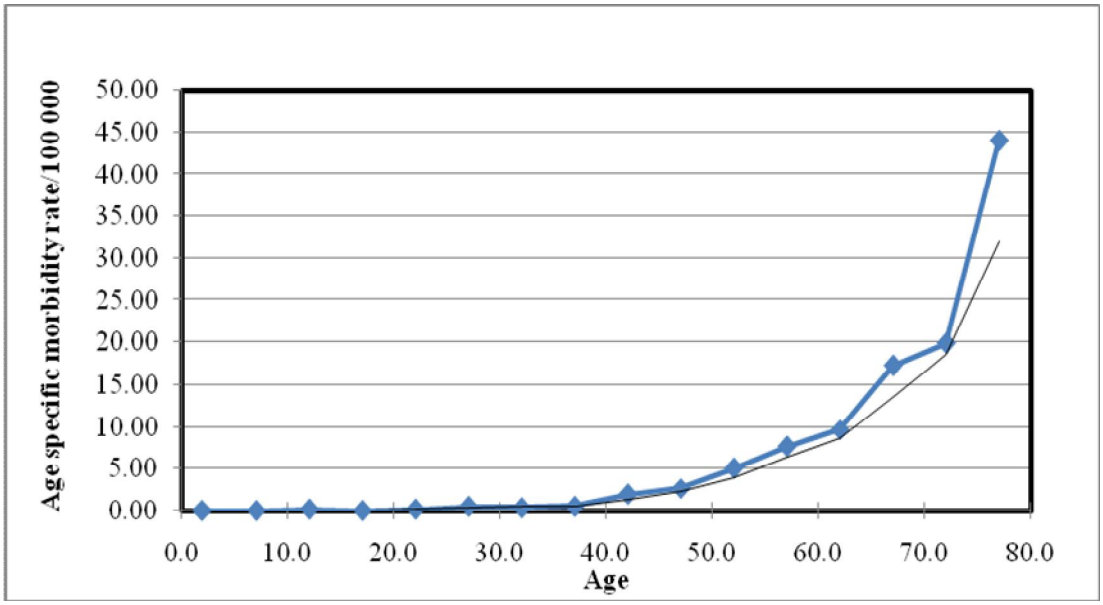

Figure 15: Line graph with trend showing age specific morbidity rate per 100 000 per year for oral & lip SCC in males

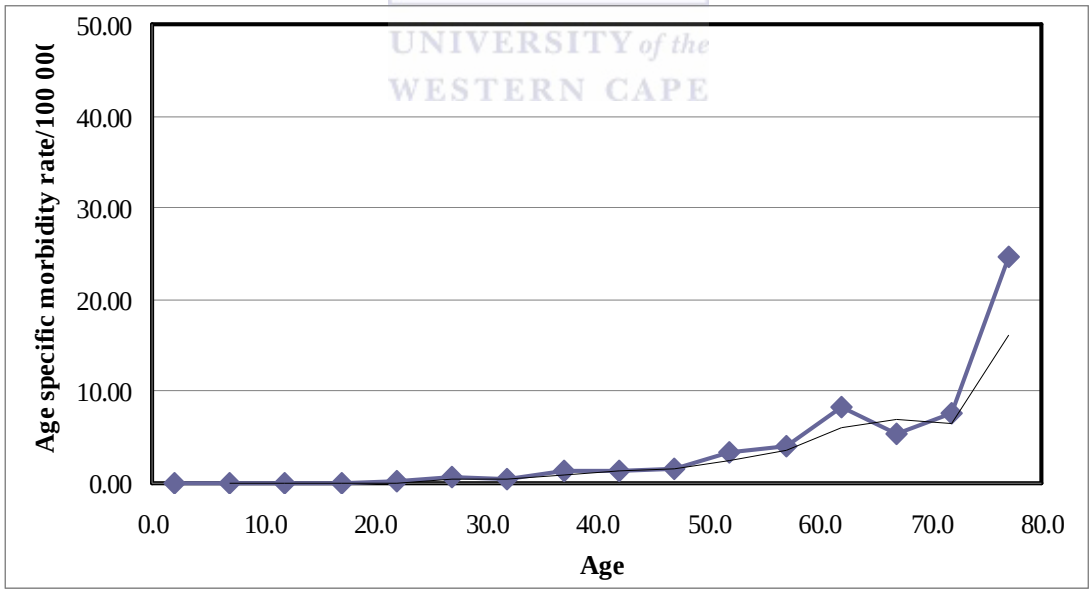

Figure 16: Line graph with trend showing age specific morbidity rate per 100 000 per year for oral & lip SCC in females

Khartoum and Gezira States incidence rates

Combined data from Khartoum and Gezira states revealed an age specific incidence rate for OSCC ranging from 0.00 to 32.47 per 100 000 for males and 0.00 to 20.00 for females. The peak age specific rate was 75+ for females and 65-69 years for males. For oral & lip SCC, the age specific rate for males ranged from 0.00 to 40.26 per 100 000 and 0.00 to 20.00 for females. Lip cancer was not contributing to oral cancer incidence in females.

ASIR for OSCC was 3.34 and 2.02 per 100 000, while for oral & lip it was 3.74 and 2.28 per 100 000 for males and females respectively.

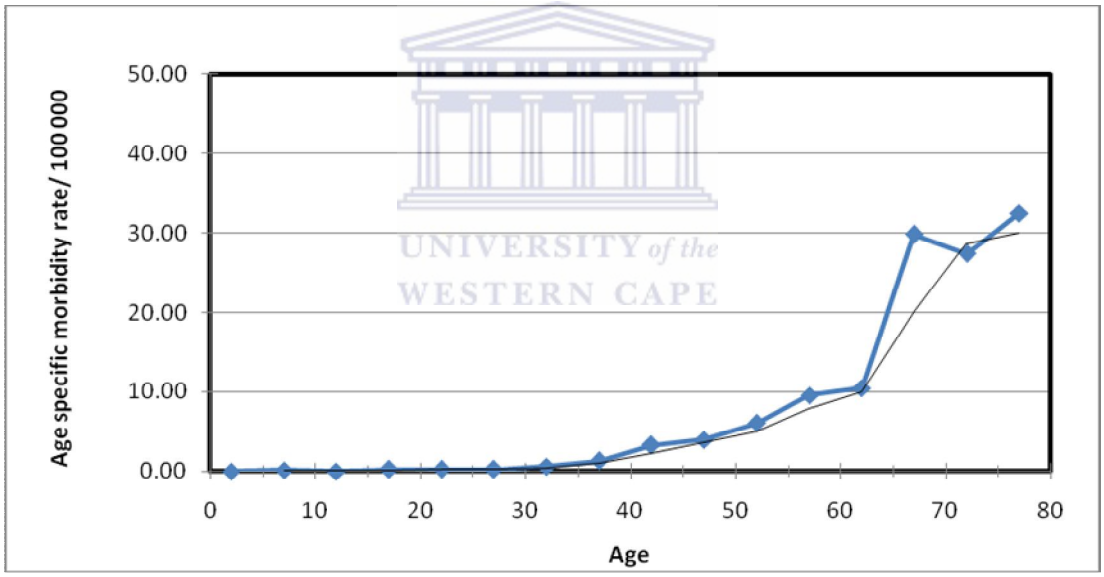

Figure 17: Age specific incidence rate with trend for OSCC for males in Khartoum and Gezira states

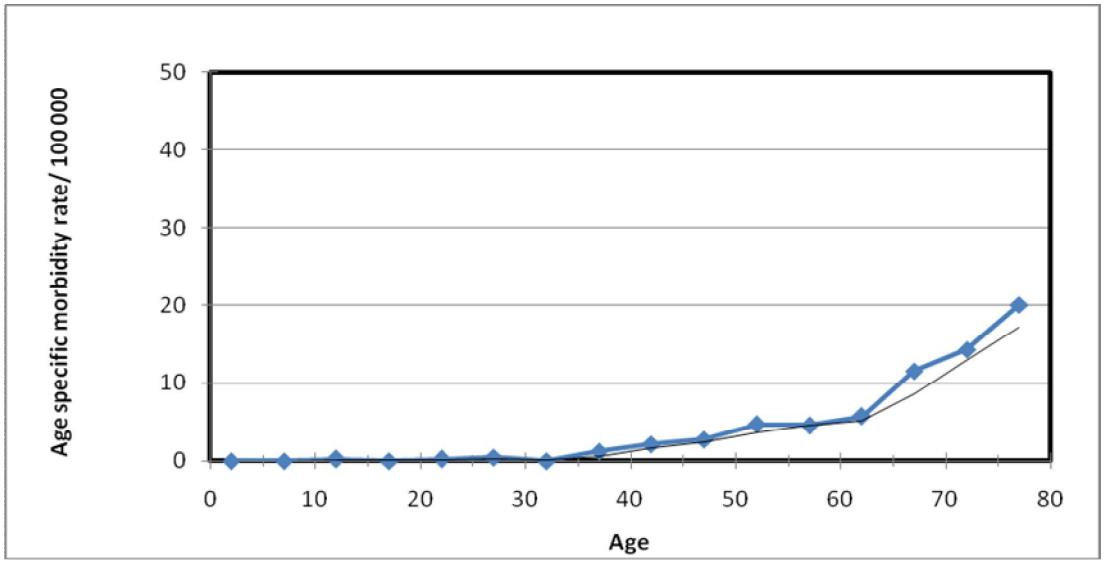

Figure 18: Age specific incidence rate with trend for OSCC for females in Khartoum and Gezira states

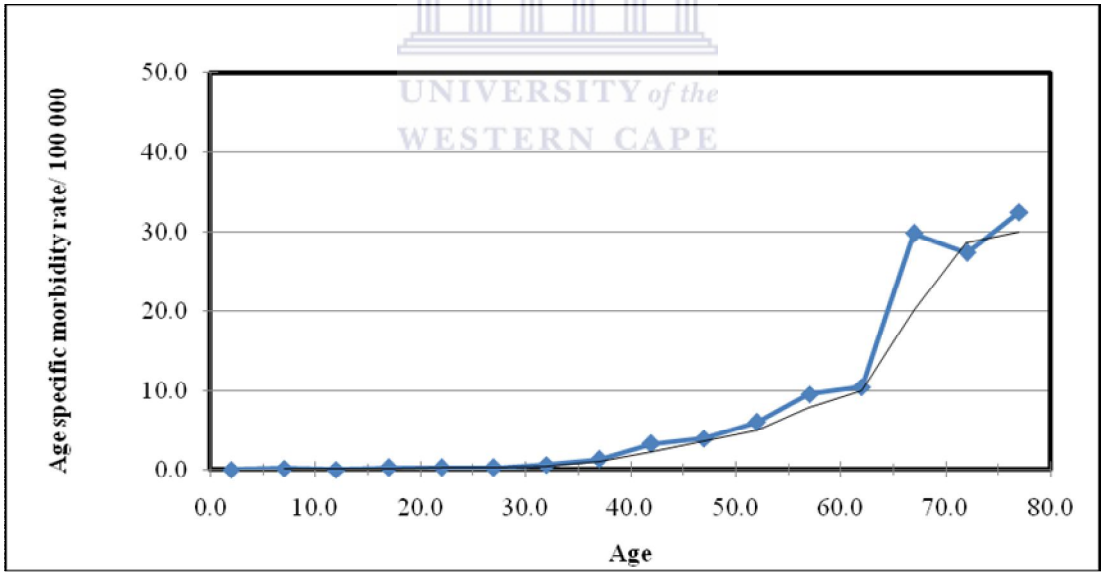

Figure 19: Age specific incidence rate with trend for oral & lip SCC for males in Khartoum and Gezira states

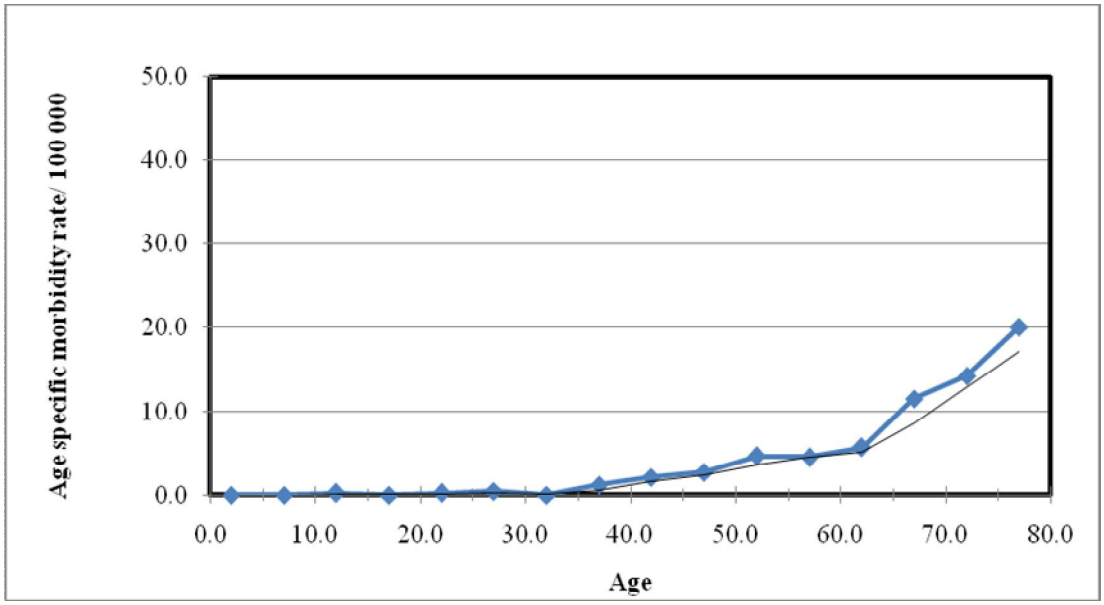

Figure 20: Age specific incidence rate with trend for oral & lip SCC for females in Khartoum and Gezira states

5.4.2 Age adjusted incidence rates

Sudanese states combined:

Table 3 shows the age adjusted incidence rate per 100 000 and the 95% confidence intervals (CI) of oral cancer for males and females. The adjusted age standardized incidence rates (ASIR) for oral & lip cancer over the study period were higher in males compared to females. The ASIRs for (OSCC/VC) was 3.19 for males and 1.83 for females (M: F =1.74:1). The ASIRs of combined oral & lip SCC/VC in Sudanese males was 3.45 and 1.88 for females (M: F=1.84:1). Lip cancer is contributing very little to the incidence of oral cancer in the Sudan and it occurs mainly in males. The ASIR of lip cancer in males was 0.30 and in females it was 0.00 per 100 000. Total intraoral malignancies showed ASIRs of 3.48 for males and 2.12 females.

Table 3: Age adjusted incidence rate per 100 000/ year for oral cancer in males and females in Sudan

	Lip	Oral SCC	Combined Oral and Lip SCC	Oral malignancies
Males	**0.30 (CI: 0.15- 0.37)**	**3.19 (CI: 2.78-3.6)**	**3.45 (CI: 3.02-3.88)**	**3.48 (CI: 3.14-3.8)**
Females	**0.00**	**1.83 (CI: 1.52-2.14)**	**1.88 (CI: 1.57- 2.19)**	**2.12 (CI: 1.79-2.24)**

Khartoum and Gezira States:

Cases from Khartoum and Gezira revealed 13% higher (4.21) ASIR for OSCC/VC in males and 11% higher (2.09) for females than the corresponding estimates for the whole country. Similarly combined oral and lip SCC/VC was 11% higher (4.18) in males and 10% higher (2.28) in females, compared to their equivalent estimates of the whole country (Table 3 and Table 4).

Table 4: Age adjusted incidence rate per 100 000/ year for oral cancer in males and females in Khartoum and Gezira states

	Oral SCC	Combined Oral and Lip SCC
Males	**4.21 (CI: 3.51-4.91)**	**4.18 (CI: 3.51- 4.97)**
Females	**2.09 (CI: 1.54- 2.64)**	**2.28 (CI: 2.28-2.28)**

5.5 *95% Confidence intervals:*

Figures 21- 25 show the ASIRs and the higher (hi) and lower (lo) limits of the 95% confidence interval for OSCC/VC, oral & lip SCC/VC and oral malignancies for both males and females.

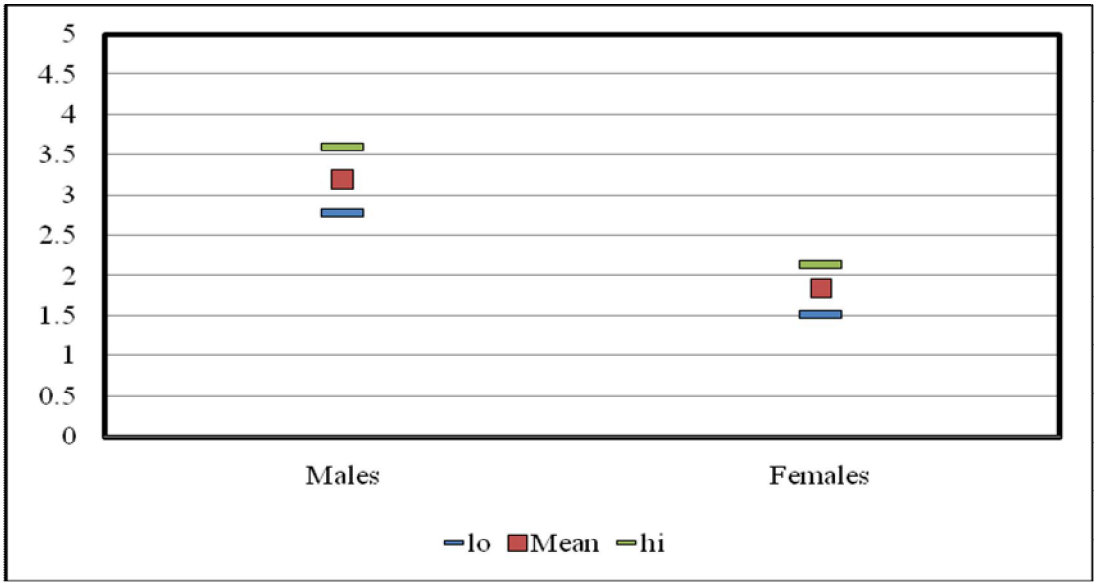

Figure 21: Depicts the ASIR per 100 000 of OSCC/VC for males and females in the Sudanese population

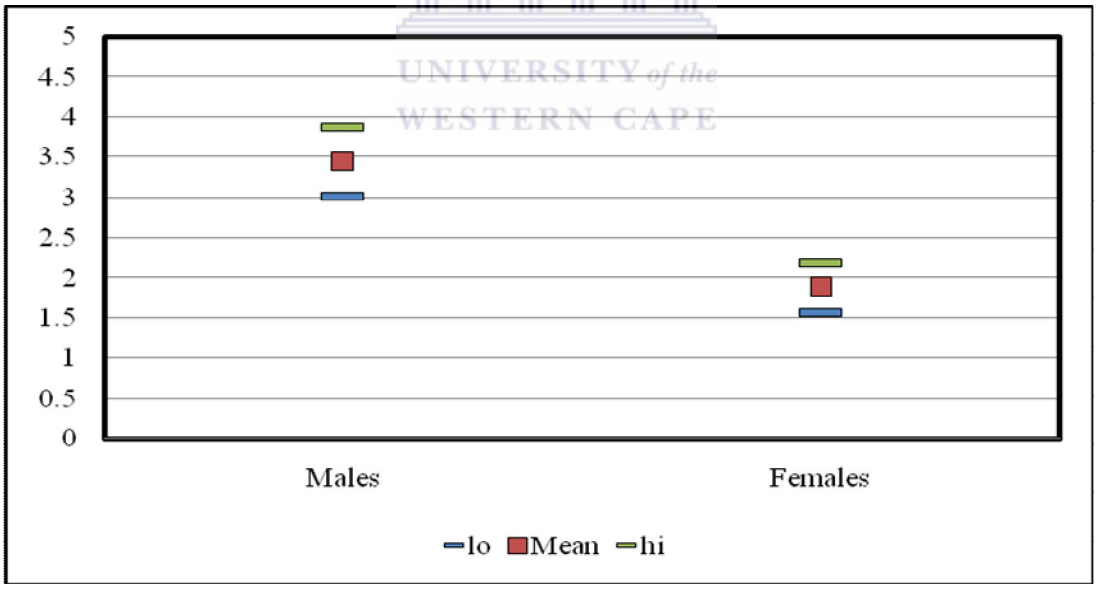

Figure 22: Depicts the ASIR per 100 000 of oral & lip SCC/VC for males and females in the Sudanese population

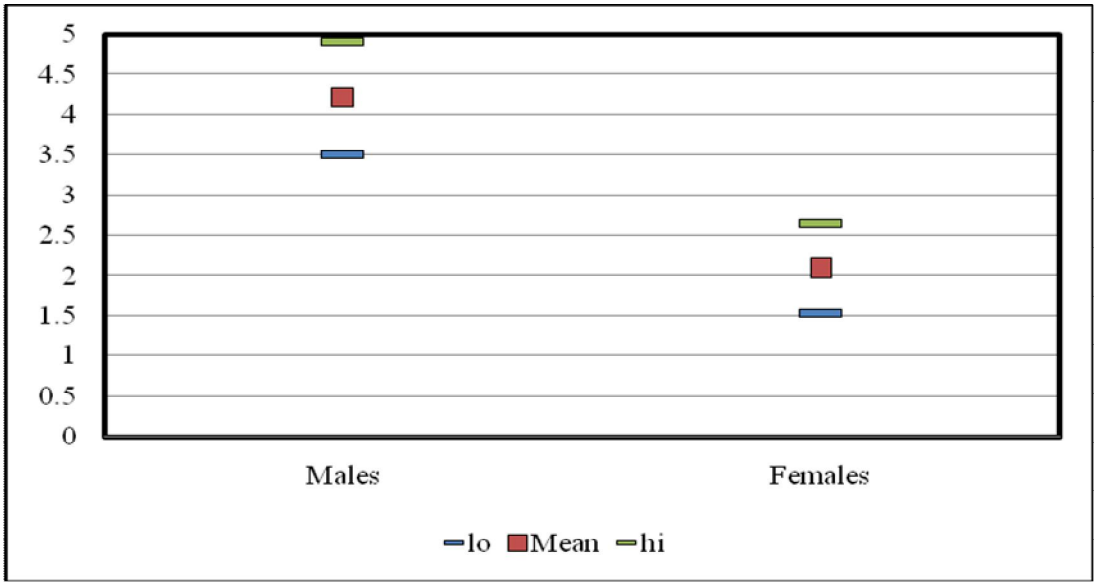

Figure 23: Depicts the ASIR per 100 000 of OSCC/VC for males and females in the Khartoum and Gezira states

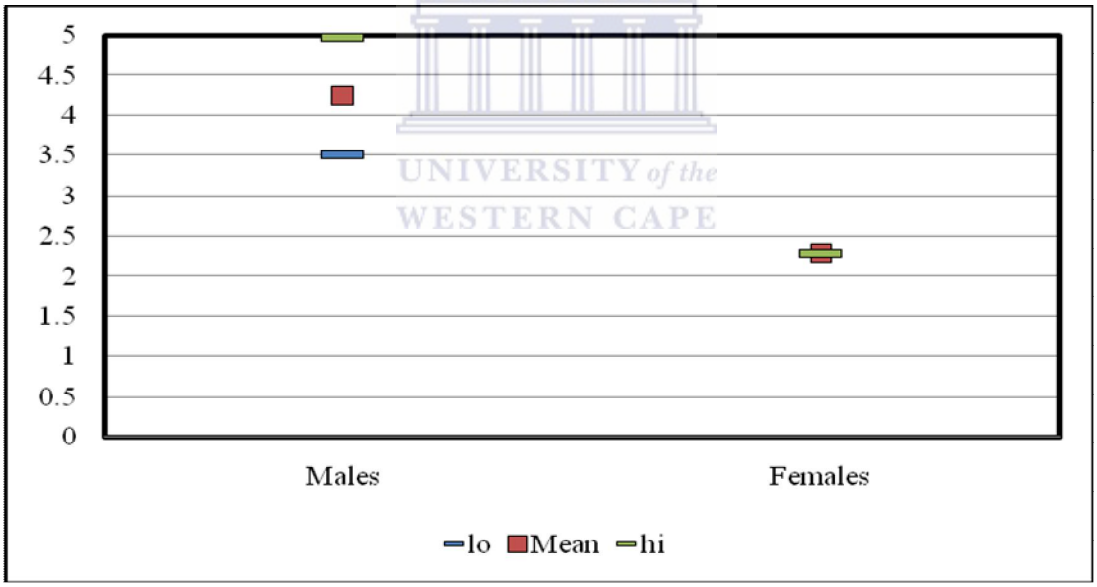

Figure 24: Depicts the ASIR per 100 000 of oral & lip SCC/VC for males and females in the Khartoum and Gezira states

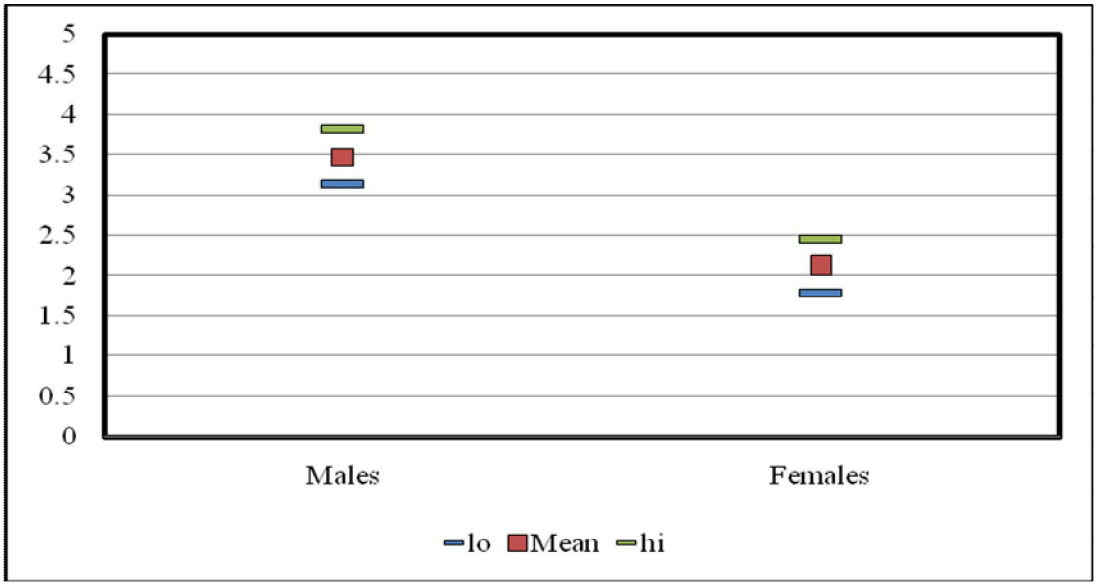

Figure 25: Depicts ASIR per 100 000 of all oral malignancies and 95% for Sudanese males and females

5.6 *Cumulative risk and cumulative rate:*

Table 5: Depicts the cumulative risk (0-74) of developing oral cancer for Sudanese males and females

	Lip	Oral SCC	Combined Oral & Lip SCC	Oral malignancies
Males	**1:438**	**1: 181**	**1: 182**	**1: 429**
Females	**-**	**1: 344**	**1: 831**	**1: 819**

Table 6: Depicts the cumulative risk (0-74) of developing oral / oral & lip SCC in Khartoum and Gezira (combined), for males and females

	Oral SCC	Combined Oral & Lip SCC
Males	**1: 616**	**1: 497**
Females	**1: 1000**	**1: 1000**

CHAPTER 6

6. DISCUSSION

Based on data from Radiation and Isotope Centre Khartoum (RICK) in Sudan; Oral cancer was one of the 10 most common cancers in males and females during the period (1967-1984), while during the period (1985-2004), this cancer was not one of the most prevalent 10 cancers in the country (Hamad, 2006).

For the total Sudanese population in 2006 of 36.3 million, 649 oral and maxillofacial (OMF) malignancies (M: F=1.44:1) were captured at KDTH during the 5-year period (2004-2008); 71% (458 cases) were intraoral malignancies; 497 cases were SCC/VC of which 390 (M: F=1.67:1) were (intra) oral squamous cancers (OSCC) and verrucous carcinomas (VC); 9% were maxillary sinus tumours (57 cases; M: F= 2.35:1); 5% (30 cases; M: F= 1.14:1) were bone tumours; 5% (30 cases; 1.14:1) were major salivary gland malignancies; 5% (35 cases; M: F= 2.88:1) lip malignancies; and 6% (39 cases; M: F= 1.44:1) were others. The latter group included lymphomas, sarcomas and malignant melanomas in addition to infrequent odontogenic malignancies.

Squamous cell carcinoma/verrucous carcinoma (SCC/VC) were the most prevalent intraoral and lip malignancies, accounting for 86% in both males and females. The ratio of oral & lip SCC/VC compared to non-SCC was 11.2: 1 (248 cases: 22 cases), and 31: 1(155 cases: 5 cases) for males and females respectively.

6.1 *Age distribution*

The age distribution of all malignancy cases during the five years revealed a gradual increase in the number of cases each decade in males and females. The average median age at diagnosis for all malignancies was 56 years for both genders and 81% of malignancy cases occurred after the age of 40. These results conform to the global epidemiology data (Warnakulasuriya, 2009) and are consistent with results of previous studies in Sudan (Osman *et al*, 2010; Idris *et al*, 1995(b)).

Oral and lip squamous cell carcinoma showed an age range from 10 to 96 years with 69.5% occurring after the age of 50 years. Lack of an increased incidence of oral cancer in ages younger than 50 years could imply lack of association of Human Papilloma Virus (HPV) in the study population. However, this is beyond the scope of the current study and further studies are needed to investigate this link. Lymphomas and sarcomas were more prevalent in ages younger than 50 years.

A sharp increase in OSCC cases in males was seen in the age group 40-44 years with a gradual increase in the number of reported cases thereafter, peaking at the eighth decade. This pattern is consistent with the distribution of the population pyramid of the mid-year of the study period. Females showed a 5 year earlier onset of OSCC compared to males. The age group 35-39 years was the period of increased oral cancer incidence with a gradual subsequent rise in the number of reported cases until peaking at the eighth decade.

SCC/VC of the lip presented over a wide age range varying from 13-80 years. 83% (25 cases) involved patients older than 50 years.

6.2 *Anatomic sites*

Malignancies involving intraoral sites collectively revealed an overall male predilection. Seventy five percent (344 cases) of intraoral SCC involved more than one anatomic site. This pattern was seen in both genders. This could reflect the late presentation of most patients after the tumour reached a very large size. Delayed clinical presentation of patients with oral cancer was documented in previous studies (Osman *et al,* 2009). Illiteracy, ignorance, poverty and lack of awareness about oral cancer plus long travel distances are contributing factors to the late presentation of patients seeking medical treatment. Osman and colleagues suggested Toombak use could be one of the reasons for this pattern of distribution of OSCC in Sudanese (Osman *et al,* 2009). However, this pattern is also prevalent in females in which the habit is far less common. However, this conclusion may be jeopardized by the fact that this habit is regarded as a social stigma in the Sudanese community in general and in females in particular. More studies are needed to investigate the reasons for the overwhelming predominance of this pattern and for the possible association with Toombak use.

Tongue cancers were the second site of intraoral malignancies with equal distribution in males and females. The estimated rate of tongue cancer for both genders was found to be 11.96% of the total oral and lip malignancies. This is significantly lower than the rate reported in the United States, which constituted 40-50% of oral cancers (Warnakulasuriya, 2009). Lifestyle and differences in risk factors involved could explain this difference in the low prevalence of tongue cancer in the Sudanese population.

Oral cancer involving the palate and the floor of mouth were the least common sites of intraoral cancer and showed equal gender distribution. The gum was also an uncommon site of intraoral cancer with increased prevalence in males with a male-to-female ratio of 1.83: 1. The habit of Toombak dipping may explain this pattern, as Toombak is mainly used by males and the most common site of placement of the Toombak dip is the labial sulcus.

SCC of the lip was generally uncommon. Our findings are consistent with other studies from Africa and Portugal (Monteiro *et al*, 2013; Kamulegeya and Kalyanyama, 2008; Marimo and Hille, 2006; Chidzonga and Mahomva, 2006). However, lip cancer prevalence showed a striking male prevalence with a M: F ratio of 2.89: 1. The habit of Toombak dipping in the lower labial sulcus in addition to sunlight damage associated with outdoor occupations, could be a reasonable explanation for the predominance of this cancer in males. It is also possible that some of the lip cancer patients presented at an advanced stage, specially cases referred from the rural regions and therefore the tumour was grouped as mouth NOS. Also placing the Toombak kid at the labial sulcus could have contributed to cancer of the gingiva and not necessarily to cancers of the mucosal site of the lip.

Malignancies involving the maxillary sinus constituted 10% of the total malignancies reported during the study period. The prevalence of these tumours showed a male-to-female ratio of 2.35: 1.

In line with previous studies published by Idris and colleagues (Idris *et al*, 1995(b)), salivary gland malignancies were the second most prevalent malignancies; accounted for 11% of the total malignant maxillofacial tumours and 5% of the intraoral

neoplasms with almost equal gender distribution (M: F= 1.14:1). Bone tumours constituted 5% of malignant cases reported with equal male and female distribution (M: F= 1.14:1).

6.3 *Incidence rates*

Calculation of the true incidence of oral cancer in Sudan is not possible unless a proper cancer registry is established in the future. Under-reporting of cancer cases in Sudan was a well-recognized phenomenon from previous studies (Hamad 2006, Idris *et al*, 1995). This research was aimed at establishing the minimum relative age standardised incidence rate of OSCC/VC for the Sudanese population during the five year study period. Data of new cancer cases reported during the period of the study was obtained from Khartoum Dental Teaching Hospital (KDTH). This still remains the main referral hospital in the country and the only hospital that offers management for oral cancer patients. Both private and governmental hospitals refer oral cancer cases to KDTH for management. Therefore in our study, due to the potential duplication of cases, no data was taken from other sources. It was also unlikely that oral cancer cases got treatment in other disciplines such as the ENT department as the maxillofacial surgeons perform all the oral cancer related surgeries.

A well-established database system for registering all oral cancer cases was only established in late 2003. This system documented all histologically diagnosed oral cancer cases referred to KDTH. The system identifies the cases based on a file number. The referring hospitals/ units and the region/ state from which the cases referred were all documented, although in some cases the regional distribution lacks proper district description which could confound the analysis of incidence data.

Therefore, data presented in this research represents the minimum oral cancer incidence documented in the main referral hospital of Sudan. As mentioned earlier under-reporting has to be acknowledged, unless a population based cancer registry is established.

Although most of the cancer registries indicate a drop of cancer incidence in the elderly, the age specific morbidity rate graphs presented in this project (Fig.13-20) reflected a steady rise at the age of 75+. This remark could be attributed to the fact that the age group 75+ constituted a relatively large proportion of the cancer cases. No breakdown of the age group 75+ was further done since the population specific data obtained from the population census that was used to calculate ASIR was designated up to 75+.

We compared our results to GLOBOCAN 2008 on oral and lip cancer, as these results are in line with the period of our study and with the same population data statistics (GLOBOCAN, 2008). Our final access to GLOBOCAN, 2008 was in November 2013. The data was subsequently updated to GLOBOCAN, 2012 and GLOBOCAN, 2008 is no longer accessible. The major change in Sudan GLOBOCAN, 2012 was that the original Sudan was split into two countries Sudan and South Sudan. Therefore the population statistics in GLOBOCAN, 2012 is different for Sudan after the political separation (GLOBOCAN, 2012).

The ASIRs of combined oral & lip SCC/VC in Sudanese males was 3.45 and 1.88 for females (M: F=1.84:1). These compare relatively well with the GLOBOCAN data which estimates a slightly lower ASIR of 3.3 for males and somewhat higher ASIR of 2.1 for females (M: F=1.57:1) (GLOBOCAN, 2008).

We also estimated ASIR for males and females for cases from Khartoum and Gezira states. These are the biggest states in Sudan with the highest population density and the closest areas to KDTH. Cases from Khartoum and Gezira revealed 13% higher (4.21) ASIR for OSCC/VC in males and 11% higher (2.09) for females than the corresponding estimates for the whole country. Similarly combined oral and lip SCC/VC is 11% higher (4.18) in males and 10% higher (2.28) in females, compared to their equivalent estimates of the whole country.

GLOBOCAN, 2012 ASIR estimates for oral and lip cancer were 4% (3.7) higher for males than the 2008 estimates, while the rates in females were only 2% (2.3) higher than the corresponding 2008 estimates. However, there appeared to be neither a clear evidence of the source nor the regional distribution of oral cancer cases in GLOBOCAN, 2012 and 2008 (GLOBOCAN, 2008; GLOBOCAN, 2012).

Table 7: Comparison of the estimated ASIR from GLOBOCAN and KDTH:

	Lip	Oral SCC	Combined Oral and Lip SCC	Oral malignancies
Males	**0.30** (CI: 0.15- 0.37)	**3.19** (CI: 2.78-3.6)	**3.45** (CI: 3.02-3.88)	**3.48** (CI: 3.14-3.8)
Females	**0.00**	**1.83** (CI: 1.52-2.14)	**1.88** (CI: 1.57- 2.19)	**2.12** (CI: 1.79-2.24)
GLOBOCAN 2008	-	-	**Males: 3.3** **Females: 2.1**	-
GLOBOCAN 2012	-	-	**Males: 3.7** **Females: 2.3**	-

These figures highlight that the population denominators and the regional distribution of cases could impact on the incidence estimates. The assumption that all cancer cases came from the different regions of the country equally may not reflect and describe the actual burden of the disease, especially in a country like Sudan that depends on a main referral hospital located in the capital. It was predicted in previous literature that some patients with oral cancer from the rural areas may die of the disease before reaching the referral hospital. This is further complicated by the erroneous perception that oral cancer is an infectious disease and people regard it as a social stigma. In addition to that many patients especially from the rural areas prefer to present to traditional healers rather than seeking medical care in hospitals.

Consideration of the regional distribution of data could also aid in tracking referral bias more precisely, in addition to having a clear picture of the distribution and the burden of oral cancer in the country, which may be influenced by environmental and climatic variety, ethnic variation or risk factors. This also alerts the government to health care intervention in problematic states or regions.

The ASIRs for oral and lip cancer derived from GLOBOCAN 2012 were consistently higher for males, females and both sexes combined in South Sudan compared to Sudan. The reason for the high estimates in South Sudan could be ascribed to the small population size, or reduced referral of oral cancer cases to Khartoum during the period of the study; the later is very plausible as the distance from Khartoum to Juba (Capital of South Sudan) is 1209.1 Kilometres, in addition to the conditions of the war which also could have been a contributing factor to diminish referral.

Sudan ASIR estimates for both males and females were slightly higher compared to other Northern African countries such as Egypt and Morocco (GLOBOCAN 2012).

The habit of Toombak dipping in the Sudanese population, especially males could explain this increase; however studies on risk factors of oral cancer in these countries could be beneficial to elucidate differences.

Compared to other African countries, Sudan's ASIR estimates for oral and lip cancer were in the mid of the curve. Countries such as Botswana and Mauritius have relatively high male ASIRs of oral and lip cancer, estimated as 8.8 and 7.4 respectively. Interestingly the two countries have strikingly lower estimates for females; 2.0 and 3.2 for Botswana and Mauritius respectively. Although a general trend of reduced ASIR estimates for female was evident in all the African countries (GLOBOCAN 2012). Unfortunately comparison of GLOBOCAN 2008 and our estimates was difficult to attain from the GLOBOCAN website.

Analysis of the geographical distribution of the cases recorded in KDTH revealed that only 5% of the cases originated from the South, compared to 28% from Khartoum state, 15% from Gezira state, 21% from the Eastern states collectively, 21% from Northern states collectively, and 9% from the Western region (Fig.11). The decrease in oral cancer reported from some of these regions could reflect difficulty of patients attending dental care units, as the majority of the cases were from either Khartoum state or neighbouring regions. However other indigenous factors that contributed to oral cancer in some of the districts were also plausible; e.g. the Northern state although far from the centre, a large percentage of cases were derived from that region. Toombak dipping is also viewed as a popular habit in males from the Northern states. The 5% of the cases from the South were probably the Southern Sudanese that live in the North.

6.4 *Cumulative risk (0-74)*

In general the estimated cumulative risks (CR) of developing oral & lip SCC/VC during a lifetime (0-74 years) were very low for both males and females (Table 5, 6; Appendix 7, 8). Lip SCC/VC has a very small impact on the CR of oral & lip SCC/VC for males, while the CR of oral & lip SCC/VC in females is markedly affected by lip cancer. Females showed markedly increased CR of oral cancer, when lip cancer was excluded from the calculation.

CHAPTER 7

7. CONCLUSION AND RECOMMENDATIONS

Oral cancer incidence data vary according to socio-political, environmental, illiteracy, lack of awareness and documentation factors. Careful interpretation of the data including the source, the exact characterization and the regional distribution could impact on the analysis. Cautious interpretation of GLOBOCAN data is required when used in healthcare planning.

Our study provides evidence that Sudan has a high relative ASIR for oral cavity and lip cancer. These incidence rate figures are higher than incidence rates reported in other African countries (Curado *et al*, 2007). There is great need for the establishment of a pathology-based national cancer registry in Sudan that ensures accurate documentation of cancer cases. A good way to start could be linking the different hospitals with a computer network that enables the documentation and registration of all oral cancer cases. There is also a need to increase dental care facilities in the peripheral areas outside the capital city to facilitate early detection and therefore decrease the burden of the disease and prevent waste of resources.

This project also highlighted that proper description of the denominators in calculation of ASIR estimates could impact significantly on interpretation of the estimates. We therefore advocate considering the regional distribution of oral cancer when estimating ASIR data whenever feasible.

Future follow up studies for site specific incidence rates are necessary to establish trends of oral cancer in Sudanese patients. More studies are needed to investigate the

reasons for the overwhelming preponderance of oral cancer cases involving more than one anatomic site.

A significant difference in oral ASIR was observed between males and females. Oral health promotion and awareness programmes regarding the risk factors, clinical presentation and signs of oral cancer are needed especially in the peripheral and rural areas. The programmes should include basic education campaigns and radio and television awareness. Introduction of oral examination as part of the general examination could also aid in early detection of oral cancer and therefore more effective and less costly treatment.

CHAPTER 8

8. LIMITATION OF THE STUDY

The time period of the study was confounded by the time when the proper database in KDTH was established and the country planning and making arrangements to separate into two countries; Sudan and South Sudan. Studies over longer duration are more helpful in establishing trends and changes in the epidemiology of oral cancer.

The data obtained in this study was the minimum number of documented cases of oral and lip cancer in the country. The true incidence rate of oral and lip cancer cannot be precisely calculated since there is no proper cancer registry in Sudan. The aim of this project was to bring to light the burden of the problem of oral cancer and to convey to the attention of the government the need and necessity for health care intervention to increase public awareness about oral cancer and risk factors especially in rural areas.

Reporting of age standardized incidence rates (ASIRs) for intraoral cancer sites combined could be misleading. e.g. in our case oral cancer involving more than one anatomic sites showed the highest prevalence, while cancer involving this distribution is less common in most other population groups. Future site specific ASIRs are required to investigate differences in distribution patterns for the different intraoral sites, which facilitate discovery of changes in oral cancer trends over the years as well as comparison to global data.

APPENDICES

Appendix 1: Ethics clearance certificate:

Office of the Deputy Dean
Postgraduate Studies and Research
Faculty of Dentistry & WHO Collaborating Centre for Oral Health

UNIVERSITY OF THE WESTERN CAPE
Private Bag X1, Tygerberg 7505
Cape Town
SOUTH AFRICA

Date: 04th July 2010

For Attention: Dr Esraa Mosalleum
Oral & Maxillo-Facial Pathology

Dear Dr Mosalleum

STUDY PROJECT: Epidemiology of oral malignancy in Sudan (2004 - 2008)

PROJECT REGISTRATION NUMBER: 10/7/20

ETHICS: **Approved**

At a meeting of the Senate Research Committee held on Friday 4th July 2010 the above project was approved. This project is therefore now registered and you can proceed with the work. Please quote the above-mentioned project title and registration number in all further correspondence. Please carefully read the Standards and Guidance for Researchers below before carrying out your study.

Patients participating in a research project at the Tygerberg and Mitchells Plain Oral Health Centres will not be treated free of charge as the Provincial Administration of the Western Cape does not support research financially.

Due to the heavy workload auxiliary staff of the Oral Health Centres cannot offer assistance with research projects.

Yours sincerely

Professor Sudeshni Naidoo

Tel -27-21-937 3148 (w); Fax -27-21-931 2287 e-mail: suenaidoo@uwc.ac.za

Appendix 2: ICD-10 Nomenclature of oral cavity topography

Malignant neoplasms of the lip, oral cavity and pharynx (C00-C14)

C00 Malignant neoplasm of lip

Excludes: skin of lip

C00.0 External upper lip

Upper lip:

NOS

Lipstick area

Vermilion border

C00.1 External lower lip

Lower lip:

NOS

Lipstick area

Vermilion border

C00.2 External lip, unspecified

Vermilion border NOS

C00.3 Upper lip, inner aspect

Upper lip:

Buccal aspect

Frenulum

Mucosa

Oral aspect

C00.4 Lower lip

Lower lip:

Buccal aspect

Frenulum

Mucosa

Oral aspect

C00.5 Lip, unspecified, inner aspect

Lip, not specified whether upper or lower:

Buccal aspect

Frenulum

Mucosa

Oral aspect

C00.6 Commisure of lip

C00.8 Overlapping lesion of lip

C00.9 Lip, unspecified

C01 Malignant neoplasm of base of tongue

Dorsal surface of base of tongue

Fixed part of tongue NOS

Posterior third of tongue

C02 Malignant neoplasm of other and unspecified parts of tongue

C02.0 Dorsal surface of tongue

Anterior two-thirds of tongue, dorsal surface

Excludes: dorsal surface of base of tongue

C02.1 Border of tongue

Tip of tongue

C02.2 Ventral surface of tongue

Anterior two-thirds of tongue, ventral surface

Frenulum linguae

C02.3 Anterior two-thirds of tongue, part unspecified

Middle third of tongue NOS

Mobile part of tongue NOS

C02.4 Lingual tonsil

Excludes: tonsil NOS

C02.8 Overlapping lesion of tongue

Malignant neoplasm of tongue whose point of origin cannot be classified to any one of the categories C01-C02.4

C02.9 Tongue, unspecified

C03 Malignant neoplasm of gum

I**ncludes**: alveolar (ridge) mucosa, gingival

Excludes: malignant odontogenic neoplasms

C03.0 Upper gum

C03.1 Lower gum

C03.9 Gum, unspecified

C04 Malignant neoplasm of floor of mouth

C04.0 Anterior floor of mouth

Anterior to the premolar-canine junction

C04.1 Lateral floor of mouth

C04.8 Overlapping lesion of floor of mouth

C04.9 Floor of mouth, unspecified

C05 Malignant neoplasm of palate

C05.0 Hard palate

C05.1 Soft palate

Excludes: nasopharyngeal surface of soft palate

C05.2 Uvula

C05.8 Overlapping lesion of palate

C05.9 Palate, unspecified

Roof of mouth

C06 Malignant neoplasm of other and unspecified parts of mouth

C06.0 Cheek mucosa

Buccal mucosa NOS

Internal cheek

C06.1 Vestibule of mouth

Buccal sulcus (upper) (lower)

Labial sulcus (upper) (lower)

C06.2 Retromolar area

C06.8 Overlapping lesion of other and unspecified parts of mouth

C06.9 Mouth, unspecified

Minor salivary gland, unspecified site

Oral cavity NO

Appendix 3: An abstract from the raw data recorded in KDTH:

Folder 2004	Year reported	Gender	Age	ICD	Ca code	Diagnosis	Occupation	Medical supervisor	State	Refferal hospital	Tribe
502	2004	M	55	C06.9	Mouth	Squamous cell carcinoma NOS	paramedical	ب/ احمد سليمان	gezira	private clinic	كواهلة
318	2004	M	38	C06.9	Mouth	Squamous cell carcinoma NOS	Driver	ب/احمد سليمان	Khartoum	not reffered	حسانية
818	2004	M	68	C06.9	Mouth	Squamous cell carcinoma NOS	Farmer	ب/احمد سليمان	Khartoum	not reffered	لا يوجد
1320	2004	M	66	C06.9	Mouth	Squamous cell carcinoma NOS	pensioner	ب/احمد سليمان	Khartoum	not reffered	شايقي
725	2004	F	50	C08.0		acinic cell carcinoma	house wife	ب/احمد سليمان	White Nile	not reffered	كواهلة
1626	2004	F	32	C06.9	Mouth	Squamous cell carcinoma NOS	house wife	ب/احمد سليمان	North	gov. hospital	كبابيش
826	2004	M	5	C06.0	Mouth	rhabdomyosarcoma	child	ب/احمد سليمان	gezira	gov. hospital	حسانية
730	2004	M	43	C06.9	Mouth	Squamous cell carcinoma NOS	Farmer	ب/احمد سليمان	Khartoum	not reffered	فلاتى
1330	2004	F	45	C41.8		osteosarcoma	off work	ب/احمد سليمان	North	not reffered	لا يوجد
1333	2004	F	79	C06.1	Mouth	Squamous cell carcinoma	house wife	ب/احمد سليمان	River Nile	not reffered	لا يوجد
635	2004	F	73	C31.0		squamous cell carcinoma	off work	م/يوسف عثمان	Khartoum	not reffered	فور
741	2004	F	40	C06.8	Mouth	adenocarcinoma	house wife	ب/احمد سليمان	Khartoum	not reffered	نوبة
441	2004	F	38	C02.8	Tongue	Squamous cell carcinoma	off work	ب/احمد سليمان	Khartoum	private clinic	بديرية
331	2004	M	44	C06.9	Mouth	Squamous cell carcinoma NOS	business	ب/احمد سليمان	Khartoum	private clinic	جعلي
759	2004	M	68	C06.9	Mouth	Squamous cell carcinoma NOS	pensioner	ب/احمد سليمان	gezira	not reffered	دنقلاوي
491	2004	M	66	C06.8	Mouth	Squamous cell carcinoma	Farmer	ب/احمد سليمان	Khartoum	not reffered	احامدة

1423	2004	M	49	C06.8	Mouth	Squamous cell carcinoma	laborer	ب/احمد سليمان	Khartoum	not reffered	جموعية
509	2004	F	73	C06.1	Mouth	Squamous cell carcinoma	house wife	م/ عبدالناصر جعفر	Khartoum	private clinic	محسي
142	2004	M	43	C31.0		squamous cell carcinoma	house wife	م/عبدالناصر جعفر	Khartoum	private clinic	حسانية
143	2004	M	73	C06.9	Mouth	Squamous cell carcinoma NOS	business	م/عبدالناصر جعفر	gezira	not reffered	لا يوجد
648	2004	M	45	C06.1	Mouth	anaplastic carcinoma	laborer	م/عبدالناصر جعفر	River Nile	gov. hospital	رباطابي
149	2004	M	19	C41.1		osteosarcoma	student	م/عبدالناصر جعفر	Khartoum	not reffered	مسيرية
150	2004	M		C31.0		squamous cell carcinoma	house wife	م/عبدالناصر جعفر	Blue Nile	not reffered	تاما
854	2004	M	25	C07	parotid	mucoepidermoid carcinoma	Driver	م/عبدالناصر جعفر	Khartoum	not reffered	مساليت
654	2004	M	65	C02.9	Tongue	Squamous cell carcinoma NOS	Farmer	م/عبدالناصر جعفر	gezira	not reffered	شكريه
360	2004	M	58	C05.8	palate	mucoepidermoid carcinoma	Farmer	م/عبدالناصر جعفر	South	not reffered	لا يوجد
161	2004	M	77	C06.9	Mouth	Squamous cell carcinoma NOS	Farmer	م/عبدالناصر جعفر	Gedarif	gov. hospital	اشراف
173	2004	F	63	C05.8	palate	Squamous cell carcinoma	house wife	م/عبدالناصر جعفر	North	gov. hospital	كبابيش
176	2004	M	68	C06.0	Mouth	Squamous cell carcinoma	off work	م/عبدالناصر جعفر	River Nile	gov. hospital	جعلي
540	2004	F	61	C06.9	Mouth	Squamous cell carcinoma NOS	house wife	م/عبدالعال محمد	Khartoum	not reffered	شايقي
1101	2004	M	71	C06.9	Mouth	Squamous cell carcinoma NOS	laborer	م/عبدالعال محمد	Khartoum	E.N.T	هندوي
601	2004	F	66	C06.9	Mouth	Squamous cell carcinoma NOS	house wife	م/عبدالعال محمد	Khartoum	not reffered	شايقي
716	2004	M	72	C04.8	floor of mouth	Squamous cell carcinoma	Farmer	م/عبدالعال محمد	Khartoum	not reffered	بديرية
519	2004	M	68	C06.9	Mouth	Squamous cell carcinoma NOS	pensioner	م/عبدالعال محمد	River Nile	not reffered	جعلي
1526	2004	F	70	C02.8	Tongue	Squamous cell carcinoma	house wife	م/عبدالعال محمد	Khartoum	not reffered	جعافرة

528	2004	F	58	C06.9	Mouth	Squamous cell carcinoma NOS	house wife	م/عبدالعال محمد	Khartoum	not reffered	مسيرية
530	2004	F	79	C06.0	Mouth	Squamous cell carcinoma	house wife	م/عبدالعال محمد	Northern	not reffered	شايقي
431	2004	F	41	C06.8	Mouth	Squamous cell carcinoma	off work	م/عبدالعال محمد	Khartoum	not reffered	جعلي
435	2004	M	63	C06.9	Mouth	Verrucous carcinoma NOS	laborer	م/عبدالعال محمد	Khartoum	Dermatology	مغاربة
542	2004	M	53	C06.9	Mouth	Squamous cell carcinoma NOS	Farmer	م/عبدالعال محمد	Khartoum	gov. hospital	جوامعة
847	2004	M	61	C00.8	Lip	Squamous cell carcinoma	Farmer	م/عبدالعال محمد	White Nile	not reffered	لا يوجد
1257	2004	F	83	C31.0		squamous cell carcinoma	house wife	م/عبدالعال محمد	Khartoum	not reffered	تنجر
462	2004	F	73	C06.9	Mouth	Squamous cell carcinoma NOS	off work	م/عبدالعال محمد	gezira	not reffered	جعلي
464	2004	F	63	C31.0		squamous cell carcinoma	house wife	م/عبدالعال محمد	Sennar	not reffered	فلاتى
1264	2004	F	73	C06.9	Mouth	Squamous cell carcinoma NOS	house wife	م/ عبدالعال محمد	Khartoum	private clinic	اشراف
465	2004	M	63	C06.9	Mouth	Squamous cell carcinoma NOS	Farmer	م/عبدالعال محمد	West	gov. hospital	لا يوجد
1266	2004	M	83	C02.8	Tongue	verrucous carcinoma	Farmer	م/عبدالعال محمد	Khartoum	not reffered	رباطابي
567	2004	M	73	C06.1	Mouth	Squamous cell carcinoma	Farmer	م/عبدالعال محمد	Khartoum	gov. hospital	دارحامد
568	2004	F	63	C07	parotid	Squamous cell carcinoma	off work	م/عبدالعال محمد	River Nile	private clinic	احامدة
671	2004	M	49	C06.9	Mouth	Squamous cell carcinoma NOS	business	م/عبدالعال محمد	Khartoum	private clinic	رشايدة
1272	2004	M	61	C31.0		squamous cell carcinoma	not	م/عبدالعال محمد	Khartoum	not reffered	لا يوجد
478	2004	F	43	C06.1	Mouth	Squamous cell carcinoma	house wife	م/عبدالعال محمد	White Nile	not reffered	كبابيش
681	2004	M	48	C96.9		lymphoma	police man	م/عبدالعال محمد	Khartoum	not reffered	جعلي
481	2004	M	39	C06.9	Mouth	Squamous cell carcinoma NOS	Farmer	م/عبدالعال محمد	River Nile	not reffered	جعلي
583	2004	M	58	C04.9	floor of	Squamous cell carcinoma NOS	not	م/عبدالعال محمد	gezira	gov. hospital	كواهلة

					mouth						
483	2004	M	58	C31.0		squamous cell carcinoma	not	م/عبدالعال محمد	Khartoum	Neurosurgery	لا يوجد
1284	2004	F	43	C06.8	Mouth	verrucous carcinoma	house wife	م/عبدالعال محمد	gezira	not reffered	دينكا
585	2004	M	41	C31.0		squamous cell carcinoma	laborer	م/عبدالعال محمد	gezira	gov. hospital	لا يوجد
592	2004	M	32	C41.1		osteosarcoma	Farmer	م/عبدالعال محمد	gezira	not reffered	رباطابي
593	2004	M	75	C00.9	Lip	Squamous cell carcinoma NOS	pensioner	م/عبدالعال محمد	Khartoum	not reffered	شايقي
5173	2004	F	48	C41.1		Squamous cell carcinoma	house wife	م/عبدالعال محمد	Khartoum	university	بنى عامر
515	2004	M	76	C06.9	Mouth	Squamous cell carcinoma NOS	shepherd	م/ عثمان الجندي	River Nile	private clinic	جعلي
415	2004	M	59	C07	parotid	mucoepidermoid carcinoma	Driver	م/ عثمان الجندى	Khartoum	Radiotherapy	حلفاوى
1131	2004	M	48	C31.0		squamous cell carcinoma	Farmer	م/ عثمان الجندي	North	gov. hospital	لا يوجد
436	2004	F	19	C41.0		adenocarcinoma	house wife	م/ عثمان الجندي	Sennar	gov. hospital	لا يوجد
547	2004	F	73	C05.0	palate	mucoepidermoid carcinoma	Farmer	م/ عثمان الجندي	Gedarif	gov. hospital	داجاوى
1364	2004	M	68	C06.9	Mouth	Squamous cell carcinoma NOS	pensioner	م/ عثمان الجندى	gezira	gov. hospital	شايقي
1464	2004	F	47	C07	parotid	Squamous cell carcinoma	laborer	م/ عثمان الجندى	Kassala	gov. hospital	جموعية
1467	2004	F	60	C00.8	Lip	Squamous cell carcinoma	laborer	م/ عثمان الجندي	Khartoum	gov. hospital	لا يوجد
1476	2004	F	53	C41.1		malignant fibrous histocytoma	house wife	م/ عثمان الجندى	North	not reffered	حسانية
689	2004	M	67	C00.8	Lip	Squamous cell carcinoma	Engineer	م/ عثمان الجندى	Khartoum	gov. hospital	مغاربة
699	2004	F	26	C83.7		Burkitt`s lymphoma	house wife	م/ عثمان الجندى	gezira	not reffered	جعلي
303	2004	F	30	C06.9	Mouth	mucoepidermoid carcinoma NOS	house wife	م/النيل احمد	Northern	not reffered	لا يوجد
312	2004	M	63	C02.8	Tongue	Squamous cell carcinoma	off work	م/النيل احمد	River Nile	not reffered	كنوز

235	2004	F	68	C06.9	Mouth	Squamous cell carcinoma NOS	house wife	م/النيل احمد	Khartoum	not reffered	لا يوجد
859	2004	M	63	C00.8	Lip	Squamous cell carcinoma	business	م/النور ابراهيم	Khartoum	Dermatology	لا يوجد
260	2004	M	6	C49.0		rhabdomyosarcoma	child	م/النيل احمد	gezira	E.N.T	مغاربة
264	2004	M	73	C06.9	Mouth	Squamous cell carcinoma NOS	shepherd	م/النور ابراهيم	West	not reffered	بديرية
379	2004	M	87	C06.9	Mouth	Squamous cell carcinoma NOS	Farmer	م/النور ابراهيم	gezira	not reffered	كواهلة
285	2004	F	48	C06.9	Mouth	Squamous cell carcinoma NOS	house wife	م/النيل احمد	North	not reffered	جوامعة
297	2004	F	68	C00.1	Lip	Squamous cell carcinoma	not	م/النيل احمد	Khartoum	not reffered	كبابيش
107	2004	M	72	C06.9	Mouth	Squamous cell carcinoma NOS	Farmer	م/محمد مرسى	Khartoum	not reffered	كواهلة
25	2004	F	8	C83.7		Burkitt`s lymphoma	not	م/محمد مرسي	Khartoum	Radiotherapy	مسلميه
42	2004	M	51	C08.9		adenoid cystic carcinoma NOS	Farmer	م/محمد مرسي	North	private clinic	حازمى
44	2004	F	35	C06.8	Mouth	Squamous cell carcinoma	house wife	م/محمد مرسي	Khartoum	private clinic	حمر
67	2004	F	63	C06.0	Mouth	Squamous cell carcinoma	house wife	م/محمد مرسي	gezira	not reffered	كبابيش

Appendix 4: Numbers of cases of intraoral squamous cell carcinoma, excluding lip cancer per age group per year for females

Table of age by year						
age	**year**					
	2004	**2005**	**2006**	**2007**	**2008**	**Total**
10-14	0 0.00	1 3.33	1 1.85	0 0.00	0 0.00	2
15-19	0 0.00	0 0.00	1 1.85	1 3.57	1 2.04	3
20-24	0 0.00	1 3.33	0 0.00	2 7.14	1 2.04	4
25-29	0 0.00	2 6.67	3 5.56	1 3.57	5 10.20	11
30-34	2	1	0	1	2	6

Frequency
Col Pct

	9.09	3.33	0.00	3.57	4.08	
35-39	2 9.09	3 10.00	4 7.41	0 0.00	6 12.24	15
40-44	4 18.18	4 13.33	1 1.85	2 7.14	4 8.16	15
45-49	1 4.55	0 0.00	6 11.11	2 7.14	3 6.12	12
50-54	0 0.00	7 23.33	2 3.70	5 17.86	5 10.20	19
55-59	1 4.55	3 10.00	6 11.11	4 14.29	1 2.04	15
60-64	3 13.64	3 10.00	7 12.96	4 14.29	10 20.41	27
65-69	2 9.09	2 6.67	4 7.41	1 3.57	1 2.04	10

70-74	5 22.73	1 3.33	7 12.96	2 7.14	0 0.00	15
75+	2 9.09	2 6.67	12 22.22	3 10.71	10 20.41	29
Total	22	30	54	28	49	183

Appendix 5: Numbers of cases of lip squamous cell carcinoma, per age group per year for males

Table of age by year					
age	**year**				
	2004	**2006**	**2007**	**2008**	**Total**
Frequency **Col Pct**					
10-14	0 0.00	1 14.29	1 9.09	0 0.00	2
25-29	0 0.00	1 14.29	0 0.00	0 0.00	1

35-39	0 0.00	1 14.29	0 0.00	0 0.00	1
40-44	0 0.00	1 14.29	0 0.00	0 0.00	1
45-49	0 0.00	0 0.00	1 9.09	0 0.00	1
50-54	0 0.00	0 0.00	3 27.27	0 0.00	3
55-59	0 0.00	2 28.57	3 27.27	2 50.00	7
60-64	2 50.00	0 0.00	2 18.18	0 0.00	4
65-69	1 25.00	0 0.00	0 0.00	0 0.00	1
70-74	0	1	0	2	3

	0.00	14.29	0.00	50.00	
75+	1 25.00	0 0.00	1 9.09	0 0.00	2
Total	4	7	11	4	26

Appendix 6: Numbers of cases of lip squamous cell carcinoma, per age group per year for females

Table of age by year

Frequency **Col Pct**	**age**	**year**					
		2004	**2005**	**2006**	**2007**	**2008**	**Total**
	35-39	0 0.00	0 0.00	0 0.00	1 33.33	0 0.00	

50-54	0 0.00	0 0.00	0 0.00	0 0.00	1 50.00	
55-59	0 0.00	0 0.00	0 0.00	1 33.33	1 50.00	
60-64	1 50.00	0 0.00	0 0.00	0 0.00	0 0.00	
65-69	1 50.00	0 0.00	0 0.00	0 0.00	0 0.00	
70-74	0 0.00	0 0.00	0 0.00	1 33.33	0 0.00	

75+	0 0.00	1 100.0 0	1 100.0 0	0 0.00	0 0.00	
Total	2	1	1	3	2	9

Appendix 7: Cumulative rate (%) of oral cancer for Sudanese males and females:

	Lip	Oral SCC	Combined Oral & Lip SCC	Oral malignancies
Males	**0.23%**	**0.55%**	**0.55%**	**0.23%**
Females	**0.00%**	**0.29%**	**0.12**	**0.12**

Appendix 8: Cumulative risk (%) of oral cancer for male and female residents in Khartoum and Gezira:

	Oral SCC	Combined Oral & Lip SCC
Males	**0.16%**	**0.2%**
Females	**0.1%**	**0.1%**

REFERENCES

Ahmed, H., G., Mahgoob, R. M., 2007. Impact of Toombak dipping in the aetiology of oral cancer: gender exclusive hazard in Sudan. *J Cancer Research*; **3**(2): 127- 30.

Altini, M., and Kola, A., H., 1985. Age specific and age standardized incidence rates for Intraoral Squamous cell carcinoma in blacks of the Witwatersrand, South Africa. *Community Dent Oral Epidemiol*; **13**(6): 334- 39.

Agrawal, N., Frederick, M., J., Pickering, C., R., Bettegowda, C., Chang, K., Li R., J., Fakhry, C., Xie, T., X., Zhang, J., Wang, J., Zhang N., El-Naggar, A., K., Jasser, S., A., , Weinstein, J., N., Treviño, L., Drummond, J., A., Muzny, D., M., Wu, Y., Wood, L., D., Hruban, R., H., Westra, W., H., Koch, W., M., Califano, J., A., Gibbs, R., A., Sidransky, D., Vogelstein, B., Velculescu, V., E., Papadopoulos, N., Wheeler, D., A., Kinzler, K., W., Myers, J., N., 2011. Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. *Science*; **333**(6046): 1154- 7.

Bánóczy, J., and Squier, C., 2004. Smoking and Disease. *Eur J Dent Educ*; **8** (4): 7- 10.

Black, R., J., Bray, F., Ferlay, J., Parkin, D., M., 1997. Cancer incidence and mortality in the European Union: cancer registry data and estimates of national incidence for 1990. *Eur J Cancer*; **33**(7): 1075- 107.

Byakodi, R., Byakodi, S., Hiremath, S., Byakodi, J., Adaki, S., Marathe, K., Mahind, P., 2012. Oral cancer in India: An epidemiologic and clinical Review. *J Community Health*; **37**(2): 316- 19.

Cawson, R. A., and Odell. W., 2008. *Cawson's essentials of oral pathology and oral medicine*. Eighth edition. Philadelphia, Elsevier.

Chaudhary, A., K., Singh, M., Sundaram, S., Methrotra, R., 2009. Role of human papillomavirus and its detection in potentially malignant and malignant head and neck lesion: updated review. *Head Neck Oncol*; **1**(1); 22. [doi: 10.1186/1758-3284-1- 22].

Chidzonga, M., M., Mahomva, L., 2006. Squamous cell carcinoma of the oral cavity, maxillary antrum and lip in a Zimbabwean population: a descriptive epidemiological study. *Oral Oncol*, **42**(2):184- 9.

Conway, D., I., Stockton, D., L., Warnakulasuriya, K., A., Ogden, G., Macpherson, L., M., 2006. Incidence of oral and oropharyngeal cancer in the United Kingdom (1990-1999) - recent trends and regional variation. *Oral Oncol*; **42**(6): 586- 92.

Costea, D., E., Lukandu, O., Bui, L., Ibrahim, M., J., Lygre, R., Neppelberg, E., Ibrahim, S., O., Vintermyr, O., K., Johannessen, A., C., 2010. *J Oral Pathol Med;* **39**(2): 128- 40.

Curado, M., P., Edwards, B., Shin H., R., Storm, H., Ferlay, J., Heanue, M., and Boyle P., eds 2007. *Cancer incidence in five continents, volume IX*. IARC Scientific Publication NO. 160, Lyon, IARC.

Curado, M. P., and Hashibe, M., 2009. Recent changes in the epidemiology of head and neck cancer. *Curr Opin Oncol*; **21**(3): 194- 200.

Davies, J., N., Wilson, B., A., Knowelden, J., 1958. Cancer in Kampala. A survey in an under-developed Country. *Brit. Med. J.;* **16**(2): 439- 43.

Djordjevic, M., V., Brunnemann, K., D., Hoffmann, D., 1993. The need for regulation of carcinogenic N- nitrosamines in oral snuff. *Food Chem Toxicol*; **31**(7): 497- 501.

Doll R., Payne P., Waterhouse J. 1966. Cancer Incidence in Five Continents: A Technical Report. Berlin: Springer- Verlag (for UICC).

Elbashir, E., I., Abeen, H., A., Idris, A., M., Abbas, K., 1989. Snuff dipping and oral cancer in Sudan: a retrospective study. *Br J Oral Maxillofac Surg*; **27**(3): 243- 8.

Gillison, M., L., D'Souza, G., Westra, W., Sugar, E., Xiao, W., Begum, S., Viscidi, R., 2008. Distinct risk factor profiles for human papillomavirus type 16-positive and negative head and neck cancer. *J Natl Cancer Inst;* **100**(6): 407- 20.

Hamad, H., M., 2006. Symposium article: Cancer initiative in Sudan. *Annals Oncol*; **17**(8): viii32- viii36.

Hecht, S., S., Hoffmann, D., 1989. The relevance of tobacco- specific nitrosamines to human Cancer. *Cancer Surv;* **8**(2): 273- 94.

Hille, J.J., Shear, M., Sitas, F., 1996. Age standardized incidence rates of oral cancer in South Africa, 1988-1991. *J Dent Assoc S Afr;* **52**(12): 771- 6.

Hoffmann, D., Adams, J., D., Lisk, D., Fisenne, I., Brunnemann, K., D., 1987. Toxic and carcinogenic agents in dry and moist snuff. *J. Natl. Cancer Inst*; **79**(6):1281- 6.

Howell, R., E., Wright B., A., and Dewar R., 2003. Trends in the incidence of oral cancer in Nova Scotia from 1983 to 1997. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; **95(2)**:205- 12.

IARC, 2006. *Smokeless tobacco, IARC Monographs on the Evaluation of carcinogenic risks to Humans;* Vol 89. Lyon: IARC.

International Agency for Research on Cancer. GLOBOCAN 2008: estimated cancer incidence, mortality and prevalence worldwide in 2008: http://globocan.iarc.fr/Default.aspx. [Last accessed November 2013].

International Agency for Research on Cancer GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012: http://globocan.iarc.fr/Default.aspx. [Last accessed February 2014].

Idris, A., M., Ahmed, H. M., Malik, M. O., 1995 (a). Toombak dipping and cancer of the oral cavity in the Sudan: a case control study. *Int J Cancer*; **63**(4): 477- 80.

Idris, A.M., Ahmed, H.M., Mukhtar, B., I., Gadir, A., F., EL-beshir, E., I., 1995(b). Descriptive epidemiology of oral neoplasms in Sudan 1970-1985 and the role of toombak. *Int J Cancer;* **61**(2): 155- 8.

Idris, A., M., Ibrahim, S., O., Vasstrand, E., N., Johannessen, A. C., Lillehaung, J., R., Magnausson, B., Wallström, M., Hirsch, J. M., Nielsen, R., 1998. The Swedish Snus and the Sudanese Toombak: are they different?. *Oral Oncol;* **34**(6): 558- 66.

Idris, A., M., Nair, J., Ohshima, H., Friesen, M., Brouet, I., Faustman E.M., Bartsch, H., 1991. Unusually high levels of carcinogenic tobacco-specific nitrosamines in Sudan snuff (Toombak). *Carcinogenesis;* **12**(6): 1115- 8.

Idris, A., M., Nair, J., Friesen, M., Ohshima H, Brouet, I., Faustman, E., M., and Bartsch, H., 1992. Carcinogenic tobacco-specific nitrosamines are present in

unusually high levels in the saliva of oral Snuff users in Sudan. *Carcinogenesis;* **13**(6), 1001- 5.

Idris, A., M., Warnakulasuriya, K., A., A., S., Ibrahim. Y., E., Nielsen, R., Cooper, D., Johanson, N., W., 1996. Toombak-associated oral mucosal lesions in Sudanese show a low prevalence of epithelial Dysplasia. *J Oral. Pathol Med;* **25** (5): 239- 44.

Idris, A., M., Ibrahim, Y., E., Warnakulasuriya, K., A., A., S., Cooper, D., J., Johnson, N., W., Nilsen, R., 1998. Toombak Use and Cigarette Smoking in the Sudan: Estimates of Prevalence in the Nile State. *Prev Med*; **27**(4): 597-603.

Johansson, S., L., Hirsch, J., M., Larsson, P., A., Saidi, J., Osterdahl, B., G., 1989. Snuff-induced Carcinogenesis: effect of snuff in rats initiated with 4- nitroquinoline-N-oxide. *Cancer Res*; **49**(6): 3063- 9.

Johnson, N. W., 1991. Orofacial neoplasms: global epidemiology, risk factors and recommendations for research. *Int Dent J;* **41**(6): 365- 75.

Kamulegeya, A., Kalyanyama, B. M., 2008. Oral maxillofacial neoplasms in an east African Population a 10 year retrospective study of 1863 cases using histopathological reports. *BMC oral Health*; 8: 19. [doi: 10.1186/1472-6831-8-19].

Leemans, C., R., Braakhuis, B., J., Brakenhoff, R., H., 2011. The molecular biology of head and neck cancer. *Nature Rev. Cancer;* **11**(2): 9– 22.

Lockart, P., B., Norris, C. M., Bulliam, C., 1998. Dental factors in the genesis of squamous cell carcinoma of the oral cavity. *Oral Oncol*; **34**(2): 133- 9.

Marimo, C., Hille, J., J., 2006. The burden of oral malignancies in Zimbabwe 1988-1997: A population based study. *Cent Afr J Med;* **52** (5-6): 51- 5.

Maufort J., P., Shai, A., Pitot, H., C., Lambert, P., F., 2010. A role for HPV 16 E5 in cervical carcinogenesis. *Cancer Res*; **70**(7): 2924- 31.

Monteiro, L., S., Antunes, L., Bento, M., J., Warnakulasuriya, S., 2013. Incidence rates and trends of lip, oral and oropharyngeal cancers in Portugal. *J Oral Pathol Med*; 42(4): 345- 51.

Osman, T., A., Satti, A, A., Bøe, O., E., Yang, Y., H., Ibrahim, S., O., Suleiman, A., M., 2010. Pattern of malignant tumours registered at a referral oral and maxillofacial hospital in Sudan during 2006-2007. *J Cancer Res Ther*; **6**(4): 473- 7.

Pannone, G., Santoro, A., Papagerakis, S., Lo Muzio, L., De Rosa, G., 2011. The role of human papilloma virus in the pathogenesis of head and neck squamous cell carcinoma: an overview. *Infect Agent Cancer*; 6: 4. [doi: 10.1186/1750-9378-6-4].

Petti, S., 2009. Lifestyle risk factors for oral cancer. *Oral Oncol*; **45**(4-5): 340- 50.

Piemonte, E., D., Lazos, J., P., Brunotto, M., 2010. Relationship between chronic trauma of the oral mucosa, oral potentially malignant disorders and oral cancer. *J Oral Pathol Med*; **39** (7): 513- 7.

Rastogi, T., Devesa, S., Mangtani, P., Mathew, A., Cooper, N., Kao, R., Sinha, R., 2008. Cancer incidence rates among South Asians in four geographic regions: India, Singapore, UK and S. *Int J Epidemiol*: **37**(1); 147- 60.

Rautava, J., Syrjänen, S., 2012. Biology of Human Papillomavirus Infections in the Head and Neck Carcinogenesis. *Head Neck Pathol*; **6**(1): S3- S15.

Rawashda, M., A., and Matalka, I., 2004. Malignant oral tumors in Jordanians, 1991-2001. A descriptive epidemiological study. *Int. J Oral Maxillofac. Surg.*, **33**(2): 183-88.

Robinson, K., L., Macfarlane, G., J., 2003. Oropharyngeal cancer incidence and mortality in Scotland: are rates still increasing?. *Oral Oncol;* **39**(1): 31- 6.

Segi M. 1960. Cancer Mortality for Selected Sites in 24 Countries (1950-57). Sendai, Tohoku University School of public health.

Sharafinski, M., E., Ferris, R., L., Ferrone, S., Grandis, J., R., 2010. Epidermal growth factor receptor targeted therapy of squamous cell carcinoma of the head and neck. *Head Neck*; **32**(10): 1412- 21.

Smith, E., M., Ritchie, J., M., Summersgill, K., F., Hoffman, H., T., Wang, D., H., Haugen, T., H., Turek, L., P., 2004. Human papillomavirus in oral Exfoliated cells and risk of head and neck cancer. *J Natl Cancer Inst*; **96**(6): 449- 55.

Stransky, N., Egloff, A., M., Tward, A., D., Kostic, A., D., Cibulskis, K., Sivachenko, A., Kryukov, G., V., Lawrence, M., S., Sougnez, C., McKenna, A., Shefler, E., Ramos, A., H., Stojanov, P., Carter, S., L., Voet, D., Cartés, M., L., Auclair, D., Berger, M., F., Saksena, G., Guiducci, C., Onofrio, R., C., Parkin, M., Romkes, M., Weissfeld, J., L., Seethala, R., R., Wang, L., Rangel-Escareño, C., Fernandez-Lopez, J., C., Hidalgo-Miranda, A., Melendez-Zajgla, J., Winckler, W., Ardlie, K., Gabriel, S., B., Meyerson, M., Lander, E., S., Getz, G., Golub, T., R., Garraway, L., A., Grandis, J., R., 2011. The mutational landscape of head and neck squamous cell carcinoma. *Science*; **333** (6046): 1157- 60.

Suba, Z., Maksa, G., Mihalayi, S., Takaea, D., 2009. Role of hormonal risk factors in oral cancer development [Article in Hungarian]. *Orv Hetil*, **150**(17): 791- 9.

Talora, C., Cialfi, S., Segatto, O., Morrone, S., Kim Choi, J., Frati, L., Paolo Dotto, G., Gulino, A., Screpanti, I., 2005. Constitutively active NOTCH1 induces growth arrest of HPV-positive cervical cancer cells via separate signalling pathways. *Exp Cell Res*; **305**(2): 343- 54.

Templeton, A. C., Buxton, E., Bianchi, A., 1972. Cancer in Kyadondo County, Uganda, 1968-1970. *J Natl Cancer Inst*, **48**(4): 865- 74.

Tapia, J., L., Goldberg, L., J., 2011. The Challenges of Defining Oral Cancer: Analysis of an Ontological Approach. *Head and Neck Pathol*; **5**(4):376– 84.

Weitkunat, R., Sanders, E., Lee, P., N., 2007. Meta-analysis of the relation between European and American smokeless tobacco and oral cancer. *BMC Public Health*; 7-334. [doi:10.1186/1471-2458-7-334].

Warnakulasuriya, K., A., Ralhan, R., 2007. Clinical, pathological, cellular, and molecular lesions caused by oral smokeless tobacco – a review. *J Oral Path Med*; **36**(2): 63- 77.

Warnakulasuriya, S., 2009. Global epidemiology of oral and oropharyngeal cancer. *Oral Oncol*, **45**(4-5): 309- 16.

Westra, W., H., 2009. The changing face of head and neck cancer in the 21st century: The impact of HPV on the epidemiology and pathology of oral cancer. *Head Neck Pathol*; **3**(1): 87- 81.

Zur Hausen, H., 2002. Papilloma viruses and cancer: from basic studies to clinical application. *Nat Rev Cancer*, **2**(5):342- 50.

World Health Organization International Classification of Disease-10. Available from: http://apps.who.int/classifications/icd10/browse/2010/en#/C00-C97. [Last accessed 12th of April, 2014].