The Incidence of Oral and Oropharyngeal Cancer in South Africa for the five year period 1997-2001

Muhammed Hanif Abram

2013

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Dedication

To my parents, Abdoolhak and Amina Abram, for teaching me the values, morals and ethics that have been the foundation of my achievements.

To my wife, Shakira, soul mate and love of my life for unwavering love and support without which I could not have completed this degree or enjoyed the pursuit of excellence within my profession.

To my children, Luqmaan, Sulaimaan and Faatimah Zahra, unknowing contributors to my degree, for giving of their precious time with Abba.
Abstract

The National Cancer Registry (NCR) of South Africa publishes pathology-based cancer incidence in the country and is the main cancer data source. The data published by the NCR have been used extensively in the development of the draft national guidelines for cancer prevention and control as well as for cancer research. The list of contributing pathology laboratories is fairly inclusive. As far as Oral Cancer is concerned, the Department of Oral Pathology, University of Limpopo, has however not submitted data to the NCR. It is therefore reasonable to assume that because of this, a large proportion of histologically diagnosed oral cancers are not reflected in the NCR. 

Materials and methods: Data from the National Cancer Registry and the University of Limpopo, Department of Oral Pathology for the five years 1997-2001 were combined and then filtered for sites in the oral and oropharyngeal region. Age-Standardised Incidence Rates (ASIR) and the Cumulative Lifetime Risk (LR) for males and females in the different population groups were determined. Conclusion: It is possible that the total ASIR for oral and oropharyngeal cancer has increased in South Africa. The incidence of oral and oropharyngeal cancer in individuals below the age of 45 years in South Africa is higher than the global average.
Contents

Chapter 1 ................................................................................................................... 7

1.1 Introduction ........................................................................................................ 7

1.2 Literature review ............................................................................................... 8

1.2.1 Terminology .................................................................................................... 8

1.2.1.1 Oral Squamous Cell Carcinoma (OSCC) and Oropharyngeal Squamous Cell
Carcinoma (OPSCC) ............................................................................................ 8

1.2.1.2 Cancer Incidence ...................................................................................... 9

1.2.2 Epidemiology ................................................................................................. 9

1.2.2.1 Asia .......................................................................................................... 11

1.2.2.2 South America and the Caribbean ......................................................... 11

1.2.2.3 European Union and Eastern European countries ................................ 12

1.2.2.4 United States of America ....................................................................... 13

1.2.2.5 Australia .................................................................................................. 13

1.2.2.6 Israel ........................................................................................................ 13

1.2.2.7 South Africa ............................................................................................. 14

1.3 Descriptive features associated with incidence data ....................................... 15

1.3.1 Migrant Studies ........................................................................................... 15

1.3.2 Age and sex ................................................................................................. 16

Chapter 2 ................................................................................................................. 17

2.1 Aim of the Study ............................................................................................... 17

2.2 Materials and Methods ..................................................................................... 17
2.3 Glossary .......................................................................................................................... 19
2.3.1 Total Population ........................................................................................................ 19
2.3.2 Crude rate .................................................................................................................... 19
2.3.3 Age standardised rate ............................................................................................... 19
2.3.4 Age specific rate .......................................................................................................... 19
2.3.5 Confidence Interval (CI) ............................................................................................ 19
2.3.6 Cumulative lifetime risk ............................................................................................ 20
2.3.7 Standard world population ......................................................................................... 20

Chapter 3 .......................................................................................................................... 21
3.1 Results ............................................................................................................................ 21
3.1.1. Age distribution of cancers ...................................................................................... 23
3.1.2. Age standardised Incidence Rate (ASIR) ................................................................. 26
3.1.3. Cumulative Lifetime Risk (LR) .................................................................................... 29
3.1.4. Incidence Rate Ratio (IRR) ......................................................................................... 30

Chapter 4 .......................................................................................................................... 32
4.1 Discussion ....................................................................................................................... 32
4.1.1 Tobacco ....................................................................................................................... 35
4.1.2 Alcohol ......................................................................................................................... 38
4.1.3 Areca Nut ..................................................................................................................... 40
4.1.4 Viral Infection ............................................................................................................. 41
4.1.5 Dietary Factors ............................................................................................................ 44
4.1.6 Genetic Factors ............................................................................................... 45

4.1.7 Material deprivation and the link with oral cancer ............................................ 46

Chapter 5 ................................................................................................................. 47

5.1 Conclusion ......................................................................................................... 47

References ............................................................................................................... 48
Chapter 1

1.1 Introduction
A number of age-standardised incidence studies of oral cancer have been done in South Africa. Some of the studies included specific race groups only, while others focused on specific geographic locations within South Africa. The National Cancer Registry (NCR) in South Africa was established in 1986. It publishes pathology-based cancer incidence in the country and is the main cancer data source. The data published by the NCR has been used extensively in the development of the draft national guidelines for cancer prevention and control as well for cancer research.

The last National Cancer Registry publication titled ‘Incidence of Histologically Diagnosed Cancer in South Africa, 1998-1999’ was published in December 2004. The list of contributing pathology laboratories, both private and institutional, is fairly inclusive. As far as oral cancer is concerned, however, the Department of Oral Pathology, University of Limpopo, had not submitted data to the NCR. It is therefore reasonable to assume that a large proportion of histologically diagnosed oral cancers are not reflected in the NCR. It is important to include these cases so as to obtain accurate figures on the incidence of oral cancer in South Africa, so the figures from the University of Limpopo were obtained separately and combined with those of the NCR.

Comprehensive reporting of cancer incidence can influence the allocation of government resources for prevention and treatment of oral and oropharyngeal cancers. The prevalence of oral cancer should justify the expense and effort required
for the implementation of national preventive strategies and to provide the necessary facilities to confirm diagnosis and provide treatment.

1.2 Literature review

1.2.1 Terminology

1.2.1.1 Oral Squamous Cell Carcinoma (OSCC) and Oropharyngeal Squamous Cell Carcinoma (OPSCC)

Oral squamous cell carcinoma (OSCC) accounts for over 95% of oral cancer lesions\(^7\,^8\). Research into the epidemiology of oral cancer is often complicated because the term ‘oral cancer’ may include a variety of anatomical sub-sites. The boundaries of the oral cavity unlike other regions of the body are often difficult to delineate. Cancer of the oral cavity and oropharynx are however, largely homogeneous in terms of descriptive epidemiology and clinical presentation\(^9\). From a clinical point of view both oral and oropharyngeal anatomical sub sites can be directly examined during routine oral health assessments. The International Classification of Diseases (ICD) is the most widely used classification of diseases. It is now in its tenth iteration\(^10\). The ICD-10 codes that are used for data collection for cancer of the various anatomical sub-sites that collectively refer to oral cancer are tabulated below.
<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>C00</td>
<td>Lip</td>
</tr>
<tr>
<td>C01</td>
<td>Base of tongue</td>
</tr>
<tr>
<td>C02</td>
<td>Other and unspecified parts of tongue</td>
</tr>
<tr>
<td>C03</td>
<td>Gum</td>
</tr>
<tr>
<td>C04</td>
<td>Floor of mouth</td>
</tr>
<tr>
<td>C05</td>
<td>Palate</td>
</tr>
<tr>
<td>C06</td>
<td>Other and unspecified parts of mouth</td>
</tr>
<tr>
<td>C09</td>
<td>Tonsil</td>
</tr>
<tr>
<td>C10</td>
<td>Oropharynx</td>
</tr>
<tr>
<td>C14</td>
<td>Other and ill defined sites in the lip, oral cavity and pharynx</td>
</tr>
</tbody>
</table>

Table 1: ICD-10 codes for oral cancer used for data collection

1.2.1.2 Cancer Incidence

“Cancer incidence” refers to the number of newly diagnosed cancers in a given time period. Cancer incidence rates are at times confused with cancer prevalence which is the number of existing cancers at any given time, irrespective of the date of diagnosis.

1.2.2 Epidemiology

It has been estimated that in the year 2002 there were 10.9 million new cases of cancer, 6.7 million deaths due to cancer, and 24.6 million persons living with cancer globally.

Cancer incidence, prevalence and distribution patterns vary widely amongst countries and within population groups. A multitude of factors determine who becomes sick, and who stays healthy. The social and physical environments that interact with the population’s genetic pool and the associated biology are important determinants of disease. These include habits such as tobacco, alcohol and drug usage; the presence of specific microorganisms and vectors; and access to and type of healthcare. The health services of developing countries are swamped by the
increasing burden of diseases, with communicable and non-communicable diseases vying for limited resources.

Amongst the leading challenges facing health care in the developing world such as human immunodeficiency virus (HIV) diseases, including acquired immune deficiency syndrome (AIDS), tuberculosis, malaria and nutritional diseases, cancer is emerging as an equally important challenge requiring urgent attention. About 5.5 million of the total cancer cases diagnosed each year are in developing countries, with approximately 60 000 new cases being reported in South Africa annually. The development of appropriate cancer control measures is dependent upon accurate reporting of cancer incidence. The information gathered through disease surveillance programmes such as cancer incidence, prevalence and geographic distribution patterns are used to evaluate the effectiveness of cancer control programmes.

More deaths are caused by cancers of the oral cavity and oropharynx than by all other diseases and disorders of the orofacial region combined. In spite of this, oral cancer has not received adequate attention from either the medical or the dental profession. This is probably owing to the focusing of the attention of the dental profession on the more common diseases of the oral cavity such and caries and periodontitis while for the medical community, oral cancer comprises a very small percentage of all cancers.

Oral cancer is the sixth most common cancer, being more common in developing than in developed countries. Worldwide, cancers of the oral cavity and oropharynx account for about 220 000 new cases per year in men (5% of all cancers) and 90 000 in women (2% of all cancers). There is a wide geographical variation in the
incidence of oral cancer. The areas of highest incidence are South and Southeast Asia, parts of Western Europe, Eastern Europe, parts of Latin America and the Caribbean and in Pacific regions\textsuperscript{14}.

\subsection*{1.2.2.1 Asia}

In parts of Asia, and in particular the Indian subcontinent, oral cancer is one of the most common forms of cancer with incidence and prevalence rates for males exceeding those for any other cancer\textsuperscript{15}. The ASIR among men in India is 12.8 per 100 000\textsuperscript{16}. In India alone over 100 000 cases of oral cancer are registered every year. The urban cancer registries in India report age-standardised incidence rates (ASIR) in different districts, for males and females together, of between 3.4 and 9.6 per 100 000 population\textsuperscript{14}. According to 2002 data, the incidence of oral cancer in females in southern Asia is relatively high with an ASIR of 8.3 per 100 000\textsuperscript{12}.

Oral cancer is one of the fastest growing malignancies in Taiwan. In 1982, its ASIR was 5.12 per 100 000 men and 1.54 per 100 000 women per year. In 2001, these rates had alarmingly increased to 27.04 per 100 000 for men and 3.17 per 100 000 for women. Oral cancer is now ranked as the leading type of cancer that causes death in Taiwanese males between the ages of 25 and 44\textsuperscript{17}.

\subsection*{1.2.2.2 South America and the Caribbean}

The country with the highest incidence of oral cancer in Latin America is Brazil. The distribution of new cases is fairly irregular throughout the states and capital cities of the country, with about 30\% of oral cancers occurring in capital cities. São Paulo has the highest ASIR for males in Latin America of 25.3 per 100 000 \textsuperscript{18,19}. The male population in Brazil has the highest risk in the world for oral cancer after those in France \textsuperscript{14}.
In the Caribbean, Puerto Rican men have the highest ASIR of 10.6 per 100 000, followed by Cuban men with an ASIR of 6.4 per 100 000\textsuperscript{20}.

### 1.2.2.3 European Union and Eastern European countries

In 2004, there were 67 000 new cases of oral and oropharyngeal cancer registered in the countries of the European Union (EU)\textsuperscript{21}, the highest male incidence rates being France and Hungary, and the lowest rates in Greece and Cyprus. The lifetime risk to Europeans of developing oral or oropharyngeal cancer is estimated at 1.85\% for men and 0.37\% for women\textsuperscript{14}. As against these overall European figures, the ASIR in France has been reported as 32.2 per 100 000 males and 4.7 per 100 000 females. The ASIR in Hungary has been reported as 22 per 100 000 males and 5 per 100 000 females\textsuperscript{14,22}. Braakhuis and co-workers analysed site-specific data collected by the Netherlands Cancer Registry for the period 1989-2006. The average number of males per year presenting with oral cancer was 315 and that of females was 221. They found an increase in the incidence of oral cancer in males of 0.5\% per year and a more pronounced increase in females of 2.0\% per year. The average number of males per year presenting with oropharyngeal cancer was 236 and that of females was 109. There was also a significant increase in the incidence of oropharyngeal cancer, 2.5\% per year for males and 3.0\% per year for females\textsuperscript{23}.

Spain has the third highest incidence rates for oral cancer in the EU\textsuperscript{24}. Portugal, Germany, Switzerland and northern regions of Italy have reported intermediate rates compared with other countries of Europe of between 10 and 20 per 100 000 \textsuperscript{14}.

In the United Kingdom, 4660 new cases of oral and pharyngeal cancer were diagnosed in 2003, accounting for 1.6\% of all cancers\textsuperscript{14}. Oral and pharyngeal cancers outnumbered uterine cervical cancer, ovarian cancer and leukaemia, singly.
The lifetime risk for developing oral cancer in the UK was 1.06% for males and 0.48% for females\textsuperscript{14}. Over the 10 year period 1990-1999, statistically significant increases of 18% and 30% in incidence were seen in males and females respectively. This trend was observed in both younger (<45 years) and older (+45 years) age groups with 3.5% and 2.4% average annual increases respectively\textsuperscript{11}. In 2009, the ASIR for males in the UK was reported as 12 per 100 000 and for females as 5.3 per 100 000\textsuperscript{22}.

1.2.2.4 United States of America

For the years 2003-2007, the ASIR was 15.4 per 100 000 men and 6.1 per 100 000 women. The age-standardised incidence of oral and pharyngeal cancer has however decreased for both males and females during the last three decades by 1.1% per year for males and 1.0% per year for females\textsuperscript{23,25}. Significant, though, is an increase in the incidence of oral cancer in the younger age groups in the US\textsuperscript{23,26}.

1.2.2.5 Australia

Abreu and co-workers\textsuperscript{27} analysed the epidemiology of oral cancer in Western Australia over the 25 year period 1982-2006. The ASIR was 14.6 and 6.2 per 100 000 for males and females, respectively. Eighty eight percent of new cases were over the age of 40, with incidence peaking in the sixth decade of life.

1.2.2.6 Israel

Zini and co-workers\textsuperscript{28} analysed the epidemiology of oral cancer in Israel over four decades – 1970-2006. They found that squamous cell carcinoma was the most common type of oral cancer with most cases occurring in men above the age of 55\textsuperscript{28}. The ASIR of oral cancer per 100 000 in Israel during these years was 7.34 among
Jewish males, 4.26 among Jewish females, 4.87 among Arab males, and 2.15 among Arab females.

1.2.2.7 South Africa

A number of age-standardised incidence studies of oral cancer that have been done in South Africa show that there is a considerable variation in the distribution of OSCC in the different population groups of this country. South African racial terminology devised by previous apartheid legislators was unscientific and was often used without justification in medical research. On the basis of racial classification, South African populations have been subjected to environments that have played an important role in determining their lifestyle, socio-economic status, residence, type of work and access to health care. These differences have played a critical role in determining the different cancer patterns observed amongst young people. Hille and co-workers analysed the ASIRs of oral cancer in South Africa over the four year period 1988-1991. They found that oral cancer accounted for 5.0% of all cancers in males and 1.8% in females. Males were affected more frequently in the black, white and coloured groups while there was a preponderance of females affected in the Asian group. The ASIR in Asian women was 6.66 per 100 000 and was higher than the ASIR for females in any of the other racial groups. The ASIR for coloured men was particularly high (13.13 per 100 000), while the ASIR for white males was 8.06 per 100 000 and that for black males 9.05 per 100 000.

The distribution of OSCC between black and white South Africans was examined by Fleming and co-workers and it was reported that the disease was more prevalent among blacks under the age of 50 when compared with whites. A significantly different age distribution was found between black and white male patients, where
33.4% of black male patients were below the age of 50 years compared to 15.6% of white males\textsuperscript{2}. In contrast, a study by Altini and co-workers\textsuperscript{1} reported that the age and gender distribution of OSCC in South African blacks conforms to the worldwide trends of intraoral cancer being a disease of the elderly and occurring most frequently in men.

A retrospective study over the period 1983-1989 of OSCC and concomitant oral habits was undertaken in South African Indians from Natal by van Wyk and co-workers\textsuperscript{5}. They found that carcinomas of the buccal mucosa were more common in women, while oropharyngeal and tongue carcinomas were more common in men. The ratio of females to males was 1.6:1, which is contrary to the ratios reported in first world countries but comparable to those reported from Bangalore and Nagpur in India\textsuperscript{5}. Bissessur and Naidoo\textsuperscript{29} reviewed the areca nut and tobacco chewing habits in Durban, Kwazulu Natal in 2009. They found that almost 60% of areca nut chewers did not know that it was harmful to their health, and the authors have therefore recommended that more aggressive awareness programmes on the dangers of areca nut chewing be instituted.

**1.3 Descriptive features associated with incidence data**

**1.3.1 Migrant Studies**

Studies on migrants and minority ethnic populations in Britain have reported significantly higher incidence rates compared to the native population in South Asian populations living in Greater London, Birmingham and Yorkshire\textsuperscript{14}. Similar incidence patterns are noted in South Africa in those of South Asian origin\textsuperscript{29}. Habit patterns such as use of betel nut and tobacco, classified as lifestyle are repeated frequently over periods of many years, rather than occasionally. Lifestyle behaviours are also
conscious choices by individuals, who might well be unaware of the consequences. Lifestyle influences are potentially reflected in the epidemiological patterns of oral cancer incidence.

### 1.3.2 Age and sex

OSCC occurs over a wide age range, with a peak of incidence in the sixth and seventh decades. From 2000 to 2004, the median age of diagnosis in the US was 62 years. In most countries, oral cancer occurs more frequently in men than in women. This may be attributable to a greater practice in risk habits by men. Globally, the ratio of males to females diagnosed with oral cancer has declined over the decades and is now about 1.5:1 for the mouth and 2.8:1 for oropharyngeal cancer.

In 2001, Llewellyn and co-workers reported that in younger persons the previous predominance of tongue cancers in males no longer prevailed, and that numerous studies had shown that tongue cancers in females outnumbered males. The reason for this may be that habits such as drinking and smoking are increasingly socially more acceptable amongst women than in the past, but studies of younger patients (arbitrarily aged less than 45 years) with oral cancers also report a high proportion of female patients with no apparent risk factors.

There is no consensus as to whether oral cancer in young people is an entity distinct from that of older people, or whether the causal factors and the course of the disease are the same as for older persons.
Chapter 2

2.1 Aim of the Study

The aim of this study is to determine the incidence of histologically diagnosed oral and oropharyngeal cancer in South Africa over the five year period 1997-2001.

2.2 Materials and Methods

Data from the National Cancer Registry (NCR) and from the University of Limpopo, Department of Oral Pathology for the five years 1997-2001 were obtained separately and then combined and filtered for sites in the oral and oropharyngeal regions. Sites included in the oral group were those reported as tongue, gingiva, floor of mouth, hard palate, soft palate, uvula, labial mucosa, buccal mucosa, retro-molar area, and any other sites described as “mouth”.

Sites included in the oropharyngeal group were those reported as pharynx, hypopharynx, oropharynx, tonsil, base of tongue and posterior third of tongue.

Lip cancers have not been included in this study because it is probable that the lip cancers recorded by the NCR include not only those arising from labial mucosa but also those from vermilion. The differing aetiological risk factors for oral cancer and for cancer of the skin and vermilion border of the lip thus preclude the use of this data in the present study.

Annual mid-term population estimates for the period by age and sex were as reported by the Actuarial Society of South Africa\textsuperscript{35}.
Incidence rates for oral and oropharyngeal cancer are reported separately. All incidence rates are reported as age-standardised per 100 000 person-years at risk. Annual mid-term population estimates for the period 1997-2001 by age and sex are as reported by the Actuarial Society of South Africa. To account for changes over time in age composition of the population, incidence rates were age-standardised using the direct method to the “standard world population”. Age-standardised incidence rates give the best insight into trends over time and are more useful for comparison between age groups and sexes.

In the present study, some of the available data was incomplete, i.e. population group, age, or sex was unknown. These data-deficient cases were proportionally allocated to the known crude incidence rates.

The cumulative lifetime risk (LR) is the probability of developing a cancer in one’s lifetime. Lifetime risk of oral and oropharyngeal cancer was calculated using the cumulative approach for those aged 0-74. The assumptions made in calculating lifetime risk are that there are no significant changes in exposure to risk factors over time, and that there are no other causes of death or other comorbidities. Clearly such assumptions are by their nature presumptions; but from the data available, these factors are imponderable.

Poisson regression models were used to assess significance of trends in incidence between the different population groups and genders. White males and white females were used as the reference groups for males and females, respectively.

Confidence intervals for the age-standardised incidence rates were based on the gamma distribution as proposed by Fay and Feuer.
2.3 Glossary

2.3.1 Total Population

As used in this study refers to the total number of people per group, cumulatively over the five year period 1997-2001.

2.3.2 Crude rate

The ratio of the number of events in the population being studied during a certain time period to the estimated population size, midway through that time period\textsuperscript{38}.

2.3.3 Age standardised rate

A method of adjusting the crude rate to eliminate the effect of differences in population age structures when comparing crude rates for different periods of time, different geographic areas and/or different population sub-groups\textsuperscript{38}.

2.3.4 Age specific rate

Age-specific disease incidence rates evaluate the occurrence of disease in proportion to a specified age group. Age-specific rates are calculated by defining the age interval, then dividing the number of disease occurrences within that interval by the total number of persons within that age interval for a particular time period\textsuperscript{39}.

2.3.5 Confidence Interval (CI)

A range of values for a variable of interest, e.g. a rate, constructed so that this range has a specified probability of including the true value of the variable. The specified probability is called the confidence level, and the end points of the confidence interval are called confidence limits\textsuperscript{40}. 
2.3.6 Cumulative lifetime risk

The probability of developing a cancer in one's lifetime.

2.3.7 Standard world population

Standard populations are "artificial populations" with fictitious age structures, that are used in age standardisation as a uniform basis for the calculation of comparable measures for the respective reference population. In the interpretation of age standardised morbidity or mortality rates it is important to notice that they are not real information in the sense of empirically observable data. In fact, they describe what the mortality or morbidity rate would be like, if the reference population and the standard population were equal, thus abstracting from age structure effects. The standard world population assumes that the groups of women and men have an identical age structure.


*This is the original source reference where this first appeared; it has been used ever since.
Chapter 3

3.1 Results

<table>
<thead>
<tr>
<th>Year</th>
<th>Female</th>
<th>Male</th>
<th>5-year total</th>
<th>Percentage of 5-year total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>23 337</td>
<td>20 543</td>
<td>57 371</td>
<td>53.62</td>
</tr>
<tr>
<td>1998</td>
<td>24 324</td>
<td>29 500</td>
<td>116 030</td>
<td>53.62</td>
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<tr>
<td>1999</td>
<td>24 059</td>
<td>29 428</td>
<td>114 103</td>
<td>53.62</td>
</tr>
<tr>
<td>2000</td>
<td>21 592</td>
<td>28 241</td>
<td>105 053</td>
<td>53.62</td>
</tr>
<tr>
<td>2001</td>
<td>22 781</td>
<td>29 851</td>
<td>116 093</td>
<td>53.62</td>
</tr>
</tbody>
</table>

Table 1. Total numbers of diagnosed cancers of all types in South Africa, 1997-2001 (All incident cases of primary cancer diagnosed by histology, cytology or haematology are recorded)

<table>
<thead>
<tr>
<th>Year</th>
<th>Female</th>
<th>Male</th>
<th>5-year total</th>
<th>Percentage of 5-year total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>29 208</td>
<td>29 499</td>
<td>58 707</td>
<td>50.16</td>
</tr>
<tr>
<td>1998</td>
<td>30 092</td>
<td>29 500</td>
<td>119 592</td>
<td>50.16</td>
</tr>
<tr>
<td>1999</td>
<td>30 480</td>
<td>29 428</td>
<td>114 508</td>
<td>50.16</td>
</tr>
<tr>
<td>2000</td>
<td>28 030</td>
<td>28 241</td>
<td>108 272</td>
<td>50.16</td>
</tr>
<tr>
<td>2001</td>
<td>29 659</td>
<td>29 851</td>
<td>119 510</td>
<td>50.16</td>
</tr>
</tbody>
</table>

Table 2. Total numbers of diagnosed cancers (excluding Basal Cell Carcinoma and Squamous Cell Carcinoma of the skin) in South Africa, 1997-2001

A total number of 293 988 new cancers were reported to the NCR in the period 1997-2001 (Table 1). Basal cell carcinoma and squamous cell carcinoma of the skin accounted for 77 222 of the cases (26.27%). The total number of cases excluding the skin was thus 216 515. Females accounted for 116 093 (53.62%) and males for 100 422 (46.38%) (Table 2). The overall male to female ratio is 0.87:1. The total male:female population ratio for the years 1997-2001 is 0.94:1.
The incidence of oropharyngeal cancer cases in South Africa for the five year period 1997-2001 is shown in Table 3. Oropharyngeal cancer in all South African males and females accounted for 0.554% and 0.132% of all cancers respectively, excluding basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin.

<table>
<thead>
<tr>
<th></th>
<th>Total 1997-2001</th>
<th>Proportion (%) to total numbers of diagnosed cancers (excluding carcinoma of the skin)</th>
<th>Male:Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian females</td>
<td>13</td>
<td>0.006</td>
<td>1.923:1</td>
</tr>
<tr>
<td>Asian males</td>
<td>25</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Black females</td>
<td>136</td>
<td>0.063</td>
<td>5.338:1</td>
</tr>
<tr>
<td>Black males</td>
<td>726</td>
<td>0.335</td>
<td></td>
</tr>
<tr>
<td>Coloured females</td>
<td>54</td>
<td>0.025</td>
<td>3.907:1</td>
</tr>
<tr>
<td>Coloured males</td>
<td>211</td>
<td>0.097</td>
<td></td>
</tr>
<tr>
<td>White females</td>
<td>85</td>
<td>0.039</td>
<td>2.788:1</td>
</tr>
<tr>
<td>White males</td>
<td>237</td>
<td>0.109</td>
<td></td>
</tr>
<tr>
<td>All females</td>
<td>286</td>
<td>0.132</td>
<td>4.192:1</td>
</tr>
<tr>
<td>All males</td>
<td>1199</td>
<td>0.554</td>
<td></td>
</tr>
</tbody>
</table>

*Table 3. Incidence of histologically diagnosed and reported cases of oropharyngeal cancer in South Africa, 1997-2001, and their proportion to all cancers (excluding Basal Cell Carcinoma and Squamous Cell Carcinoma of the skin)*

The incidence of oral cancer cases in South Africa for the five year period 1997-2001 is shown in Table 4. Oral cancer in all South African males and females respectively accounted for 1.913% and 0.614% of all cancers, excluding basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin.
<table>
<thead>
<tr>
<th></th>
<th>Total 1997-2001</th>
<th>Proportion (%) to total numbers of diagnosed cancers (excluding carcinoma of the skin)</th>
<th>Male:Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asian females</strong></td>
<td>80</td>
<td>0.037</td>
<td>0.888:1</td>
</tr>
<tr>
<td><strong>Asian males</strong></td>
<td>71</td>
<td>0.033</td>
<td></td>
</tr>
<tr>
<td><strong>Black females</strong></td>
<td>576</td>
<td>0.266</td>
<td>4.394:1</td>
</tr>
<tr>
<td><strong>Black males</strong></td>
<td>2531</td>
<td>1.169</td>
<td></td>
</tr>
<tr>
<td><strong>Coloured females</strong></td>
<td>201</td>
<td>0.093</td>
<td>2.891:1</td>
</tr>
<tr>
<td><strong>Coloured males</strong></td>
<td>581</td>
<td>0.268</td>
<td></td>
</tr>
<tr>
<td><strong>White females</strong></td>
<td>472</td>
<td>0.218</td>
<td>2.030:1</td>
</tr>
<tr>
<td><strong>White males</strong></td>
<td>958</td>
<td>0.442</td>
<td></td>
</tr>
<tr>
<td><strong>All females</strong></td>
<td>1329</td>
<td>0.614</td>
<td>3.116:1</td>
</tr>
<tr>
<td><strong>All males</strong></td>
<td>4141</td>
<td>1.913</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Incidence of histologically diagnosed and reported cases of oral cancer in South Africa, 1997-2001, and their proportion to all cancers (excluding Basal Cell Carcinoma and Squamous Cell Carcinoma of the skin)

3.1.1. Age distribution of cancers

The age specific incidence rates per 100 000 were calculated from the combined data from the National Cancer Registry (NCR) and the University of Limpopo, Department of Oral Pathology for the five years 1997-2001. Data for each race and gender group was stratified into age intervals of 5 years (e.g. 0-5, 5-10, 10-15, etc.). Age-specific rates were calculated by dividing the number of cancer incidences within that age interval by the total number of persons within that age interval for the five year period.
This data was then used to calculate the proportion of those cases less than 45 years old to all cases in each specific race and gender group.

**Oropharyngeal cancer**

Males below 45 years of age comprised 5.200% of all male cases, whereas females below 45 years of age comprised 11.170% of all female cases.

There is therefore a greater incidence of oropharyngeal cancer in younger females below 45 years old when compared to younger males. The incidence of oropharyngeal cancer in younger females is also greater than the incidence of oral cancer in both younger males and females.

<table>
<thead>
<tr>
<th>Race/Gender</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian females</td>
<td>10.900</td>
</tr>
<tr>
<td>Asian males</td>
<td>2.600</td>
</tr>
<tr>
<td>Black females</td>
<td>8.440</td>
</tr>
<tr>
<td>Black males</td>
<td>5.980</td>
</tr>
<tr>
<td>Coloured females</td>
<td>11.450</td>
</tr>
<tr>
<td>Coloured males</td>
<td>5.550</td>
</tr>
<tr>
<td>White females</td>
<td>8.050</td>
</tr>
<tr>
<td>White males</td>
<td>7.510</td>
</tr>
<tr>
<td>Total males</td>
<td>5.200</td>
</tr>
<tr>
<td>Total females</td>
<td>11.170</td>
</tr>
</tbody>
</table>

*Table 5. Proportion of cases below 45 years of age to all cases in group for oropharyngeal squamous cell carcinoma for the five year period 1997-2001.*
Oral cancer

Males below 45 years of age comprised 7.280% of all male cases, whereas females below 45 years of age comprised 7.840% of all female cases.

<table>
<thead>
<tr>
<th></th>
<th>Proportion %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian females</td>
<td>4.780</td>
</tr>
<tr>
<td>Asian males</td>
<td>0.000</td>
</tr>
<tr>
<td>Black females</td>
<td>8.150</td>
</tr>
<tr>
<td>Black males</td>
<td>6.970</td>
</tr>
<tr>
<td>Coloured females</td>
<td>7.840</td>
</tr>
<tr>
<td>Coloured males</td>
<td>5.890</td>
</tr>
<tr>
<td>White females</td>
<td>9.400</td>
</tr>
<tr>
<td>White males</td>
<td>8.590</td>
</tr>
<tr>
<td>Total males</td>
<td>7.280</td>
</tr>
<tr>
<td>Total females</td>
<td>7.840</td>
</tr>
</tbody>
</table>

*Table 6 Proportion of cases below 45 years of age to all cases in group for oral squamous cell carcinoma for the five year period 1997-2001.*
3.1.2. Age standardised Incidence Rate (ASIR)

The ASIRs of oral squamous cell carcinoma (OSCC) and oropharyngeal squamous cell carcinoma (OPSCC) for both genders in the different population groups in South Africa for the five year period 1997-2001, are expressed as the number of cases per 100 000 population, standardised against a standard world population\textsuperscript{36}.

The ‘direct’ method of standardization involves calculating from each of the age specific rates the expected number of cases that would occur in the standard world population. The standard world population adds up to 100 000, therefore the sum of the expected cases is the age-standardised rate of the population studied.

Tables 7 and 8 show the ASIR for oropharyngeal cancer in males and females, respectively. ASIR is highest for coloured males being more than twice that of any other race group.

Among females the ASIR is highest for coloureds. White females have the second highest ASIR followed closely by Asian females.

The population group with the highest ASIR for OPSCC for both genders is the coloured group.
<table>
<thead>
<tr>
<th>Race</th>
<th>Total cases oropharyngeal cancer reported - males</th>
<th>Total population over 5-year period</th>
<th>Crude rate</th>
<th>Age standardised rate</th>
<th>Lower confidence interval</th>
<th>Upper confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>25</td>
<td>2784714</td>
<td>0.898</td>
<td>1.322</td>
<td>0.84</td>
<td>2.148</td>
</tr>
<tr>
<td>Black</td>
<td>726</td>
<td>831000000</td>
<td>0.873</td>
<td>1.678</td>
<td>1.555</td>
<td>1.813</td>
</tr>
<tr>
<td>Coloured</td>
<td>211</td>
<td>9596217</td>
<td>2.199</td>
<td>3.805</td>
<td>3.288</td>
<td>4.404</td>
</tr>
<tr>
<td>White</td>
<td>237</td>
<td>115000000</td>
<td>2.065</td>
<td>1.704</td>
<td>1.493</td>
<td>1.946</td>
</tr>
</tbody>
</table>

Table 7. ASIR per race group for oropharyngeal squamous cell carcinoma in the male South African population for the five year period 1997-2001

<table>
<thead>
<tr>
<th>Race</th>
<th>Total cases oropharyngeal cancer reported - females</th>
<th>Total population over 5-year period</th>
<th>Crude rate</th>
<th>Age standardised rate</th>
<th>Lower confidence interval</th>
<th>Upper confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>14</td>
<td>2864524</td>
<td>0.474</td>
<td>0.519</td>
<td>0.276</td>
<td>0.982</td>
</tr>
<tr>
<td>Black</td>
<td>135</td>
<td>888000000</td>
<td>0.152</td>
<td>0.23</td>
<td>0.192</td>
<td>0.274</td>
</tr>
<tr>
<td>Coloured</td>
<td>55</td>
<td>101000000</td>
<td>0.543</td>
<td>0.732</td>
<td>0.548</td>
<td>0.966</td>
</tr>
<tr>
<td>White</td>
<td>84</td>
<td>120000000</td>
<td>0.702</td>
<td>0.549</td>
<td>0.437</td>
<td>0.694</td>
</tr>
</tbody>
</table>

Table 8. ASIR per race group for oropharyngeal squamous cell carcinoma in the female South African population for the five year period 1997-2001
Table 9. ASIR per race group for oral squamous cell carcinoma in the male South African population for the five year period 1997-2001

<table>
<thead>
<tr>
<th>Race</th>
<th>Total cases oral cancer reported – males</th>
<th>Total population over 5-year period</th>
<th>Crude rate</th>
<th>Age standardised rate</th>
<th>Lower confidence interval</th>
<th>Upper confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>71</td>
<td>2784714</td>
<td>2.549</td>
<td>3.217</td>
<td>2.46</td>
<td>4.281</td>
</tr>
<tr>
<td>Black</td>
<td>2531</td>
<td>83100000</td>
<td>3.045</td>
<td>5.823</td>
<td>5.59</td>
<td>6.067</td>
</tr>
<tr>
<td>Coloured</td>
<td>581</td>
<td>9596217</td>
<td>6.052</td>
<td>10.164</td>
<td>9.32</td>
<td>11.088</td>
</tr>
<tr>
<td>White</td>
<td>958</td>
<td>11500000</td>
<td>8.347</td>
<td>6.849</td>
<td>6.419</td>
<td>7.309</td>
</tr>
</tbody>
</table>

Table 10. ASIR per race group for oral squamous cell carcinoma in the female South African population for the five year period 1997-2001

<table>
<thead>
<tr>
<th>Race</th>
<th>Total cases oral cancer reported – females</th>
<th>Total population over 5-year period</th>
<th>Crude rate</th>
<th>Age standardised rate</th>
<th>Lower confidence interval</th>
<th>Upper confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>80</td>
<td>2864524</td>
<td>2.799</td>
<td>3.382</td>
<td>2.667</td>
<td>4.291</td>
</tr>
<tr>
<td>Black</td>
<td>576</td>
<td>88800000</td>
<td>0.649</td>
<td>1.005</td>
<td>0.923</td>
<td>1.092</td>
</tr>
<tr>
<td>Coloured</td>
<td>201</td>
<td>10100000</td>
<td>1.99</td>
<td>2.801</td>
<td>2.419</td>
<td>3.231</td>
</tr>
<tr>
<td>White</td>
<td>472</td>
<td>12000000</td>
<td>3.944</td>
<td>2.806</td>
<td>2.549</td>
<td>3.091</td>
</tr>
</tbody>
</table>

Tables 9 and 10 show the ASIR for oral cancer in females and males, respectively. ASIR is highest for coloured males followed by white males. Among females ASIR is highest for Asians. Of particular note is that there is a male preponderance among blacks, coloureds and whites but females are affected more frequently among
Asians. White females have the second highest ASIR followed closely by coloured females.

The ASIR for OSCC is higher than that for OPSCC in all groups.

### 3.1.3. Cumulative Lifetime Risk (LR)

<table>
<thead>
<tr>
<th>GENDER</th>
<th>ASIAN</th>
<th>BLACK</th>
<th>COLOURED</th>
<th>WHITE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1:1628</td>
<td>1:3878</td>
<td>1:1160</td>
<td>1:1430</td>
</tr>
<tr>
<td>Male</td>
<td>1:512</td>
<td>1:483</td>
<td>1:212</td>
<td>1:460</td>
</tr>
</tbody>
</table>

*Table 11. LR for developing oropharyngeal squamous cell carcinoma in the South African population, based on 1997-2001 data.*

<table>
<thead>
<tr>
<th>GENDER</th>
<th>ASIAN</th>
<th>BLACK</th>
<th>COLOURED</th>
<th>WHITE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1:217</td>
<td>1:847</td>
<td>1:314</td>
<td>1:309</td>
</tr>
<tr>
<td>Male</td>
<td>1:260</td>
<td>1:144</td>
<td>1:78</td>
<td>1:123</td>
</tr>
</tbody>
</table>

*Table 12. LR for developing oral squamous cell carcinoma in the South African population, based on 1997-2001 data*

The LR for developing both OSCC and OPSCC is highest for coloured males and lowest for black females.
3.1.4. Incidence Rate Ratio (IRR)

Using Poisson regression models the IRR was calculated with whites as the reference group.

<table>
<thead>
<tr>
<th>Oropharynx Poisson regression models</th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>coef</td>
<td>se</td>
<td>IRR</td>
<td>coef</td>
</tr>
<tr>
<td>Asian</td>
<td>-0.374*</td>
<td>0.221</td>
<td>0.688</td>
<td>-0.048</td>
</tr>
<tr>
<td>Black</td>
<td>-0.009</td>
<td>0.079</td>
<td>0.991</td>
<td>-0.793***</td>
</tr>
<tr>
<td>Coloured</td>
<td>0.780***</td>
<td>0.100</td>
<td>2.182</td>
<td>0.338**</td>
</tr>
</tbody>
</table>

*Table 13.*

**note:** *** p<0.01, ** p<0.05, * p<0.1

The IRR of OPSCC in coloured males was significantly greater than that of whites (p<0.01) whereas in coloured females it was significantly greater than that of whites (p<0.05). The IRR of OPSCC in black females was significantly less than that of whites (p<0.01).
The IRR of OSCC in coloured males was significantly greater than that of whites (p<0.01) whereas in Asian and black males, as well as black females it was significantly less than that of whites (p<0.01).

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>coef</td>
<td>se</td>
</tr>
<tr>
<td>Asian</td>
<td>-0.728***</td>
<td>0.135</td>
</tr>
<tr>
<td>Black</td>
<td>-0.161***</td>
<td>0.042</td>
</tr>
<tr>
<td>Coloured</td>
<td>0.392***</td>
<td>0.058</td>
</tr>
</tbody>
</table>

*Table 14*

Note: *** p<0.01, ** p<0.05, * p<0.1
Chapter 4

4.1 Discussion

Oral health is central to our daily life and well-being, and exerts a fundamental influence on the quality of life of every citizen of South Africa. A multitude of factors influence oral health. These include daily activities such as tooth brushing, the foods we eat and choice of sexual practices.

Oral health is more than just the absence of disease or loss of function. People are increasingly aware that the optimal functioning of their face and mouth is important for their own comfort and for preserving their self-esteem. Individuals and communities have to be made aware of the risk factors that cause oral diseases and how they can be involved in preventing or eliminating these risks. They can be informed through outreach projects, health education and health promotion. Oral health problems can in most cases be prevented, and is thus a public health concern needing involvement of the private and public sectors.

Oral cancer is the most important oral disease in terms of its severe morbidity and high mortality. Pathology-based rates probably underestimate the true burden of oral cancer in South Africa. Analysis of available data reflects minimal incidence rates of the disease because only oral cancers that are diagnosed with pathological confirmation are listed in the National Cancer Registry; but those without pathological confirmation, for example, cancers diagnosed only clinically, radiographically, or recorded only on death certificates, are not listed by the NCR\(^6\) and therefore, of course, not included in the present study.
In the South African context, the different racial groups have in the past been subjected to different environments by the Group Areas Act of the previous apartheid government. These environments played an important role in determining their lifestyle, socio-economic status, place and type of residence, type of work and access to health care. Under the more recent political dispensation, for some these factors have hardly changed.

In this study, we have calculated the age-specific and age-standardised incidence rates of oral and oropharyngeal cancers separately.

The ASIR of OSCC was greater than that of OPSCC in all groups. The ASIR for OSCC is significantly higher for coloured males (10.164) than for any other group. Among females ASIR is highest for Asians (3.382). Of particular note is that there is a male preponderance among blacks, coloureds and whites but females are affected more frequently among Asians. The ASIR for Asian females (3.382) in South Africa is however significantly lower than the ASIR for Asian females in south Asia (8.3)\(^1\). White females have the second highest ASIR followed closely by coloured females.

ASIR for OPSCC is highest for coloured males. The ASIR in coloured males (3.805) is more than twice that of any other race group. Among females the ASIR for OPSCC is highest for coloureds (0.732). White females have the second highest ASIR followed closely by Asian females. The population group with the highest ASIR for OPSCC for both genders is the coloured group.

The ASIRs for OSCC for all groups are slightly lower than those reported by Hille and co-workers over the 4 year period 1988-1991\(^2\). Compared to the ASIR of OSCC for coloured males reported by Breytenbach (1979)\(^3\) the ASIR for coloured males (10.164) is slightly higher\(^2\). The ASIR of OSCC for black males (5.823) is marginally
higher than those reported by Altini and Kola (1985)\textsuperscript{1}. It is possible that the total ASIR for oral and oropharyngeal cancer has increased in South Africa. By separating the ASIR of oropharyngeal cancer from that of oral cancer, structures such as the base of tongue are not included in the oral cancer data, and may therefore result in lower ASIR for oral cancer when compared to other studies that have included all cancers within the oral and oropharyngeal regions collectively.

When compared to international ASIRs, the ASIR for coloured males for OSCC (10.164) is similar to that of Puerto Rican males (10.6) as reported by Suarez (2009)\textsuperscript{20}. It is however lower than that for males in Western Australia (14.6), USA (15.4), and France (32.2)\textsuperscript{14,25,27}.

About 6\% of oral cancers occur in young people under the age of 45 years\textsuperscript{31}. Our data reveals that in South African males, 7.276\% of all cases occurred in those below 45 years old. In South African females, 7.844\% of all cases occurred in those below 45 years old. With regard to OPSCC our data reveals that Asian females and coloured females have a higher proportion of incidence in the younger (i.e.<45 year old) age group, viz. 10.9\% and 11.45\% respectively. The incidence of oropharyngeal cancer in younger females is also higher than the incidence of oral cancer in both younger males and females.

The Cumulative Life Time Risk (LR) for developing oral cancer for coloured males is very high (1:78) (Table 12) and is greater than the LR for colorectal cancer (1:97) as well as bladder cancer (1:108) for the same racial group, whereas the LR for lung cancer is higher at 1:69. \textsuperscript{6} The LR for oropharyngeal cancer for coloured males (1:212) is also extremely high when compared to the LR for all other groups. This indicates that coloured males probably have significantly higher exposure to risk.
factors for oral and oropharyngeal cancer than do other racial groups. Excepting LR for oral cancer in Asian males, males of all population groups have higher LR than females, for both oral and oropharyngeal cancer, suggesting that overall, females have a lower exposure to risk factor behaviour. However, Asian females, on the other hand, have a higher LR for developing oral cancer than do Asian males, implying higher exposure to risk factor behaviour by females of this group.

Striking variations in the risk of different cancers between population groups exist, and these can be attributed to known or suspected risk factors related to lifestyle or environment. It has been estimated that 43% of cancer deaths worldwide are owing to tobacco usage, dietary factors and infections\textsuperscript{15}. Amongst the implicated infective agents for oral cancer are human papilloma virus, Epstein Barr virus, and Candida albicans. Other suspected aetiological agents include areca (betel nut) chewing, diets low in carotenoids and vitamin A, and poor dento-gingival bacterial plaque control\textsuperscript{42,43}. Low-income and disadvantaged groups are generally more exposed to avoidable risk factors such as environmental carcinogens, alcohol, infectious agents and tobacco use. Review of the aetiological risk factors for oral and oropharyngeal cancer is necessary so that trends in cancer incidence could possibly be tied down to behavioural and demographic risk factors. This could furthermore provide a basis for the assessment of the efficacy of current preventive measures in an attempt to curb the growing prevalence of oral cancer.

4.1.1 Tobacco

Tobacco is defined as any preparation of the leaves of plants of the genus \textit{Nicotiana}, of the nightshade family. Nicotine, which is the main psychoactive alkaloid of tobacco, constitutes only about 5% of the total dry weight of the plant leaves.
Nicotine functions by binding to nicotinic acetylcholine receptors, causing increased heart rate, vasoconstriction and alertness. Nicotine produces dependence among genetically, mentally, and socially predisposed individuals\textsuperscript{30}. Tobacco was already known about 13 500 years ago in south Chile. It has been used by native Americans and Australian aborigines for ritualistic, medicinal, and therapeutic applications. Its capacity to ameliorate the awareness of hunger, thirst, fatigue, fear and cold constitutes the primary reason for its extensive use.

From these ancient origins, tobacco consumption has now reached global epidemic status. Global data on the prevalence of cigarette smoking show that almost one billion men in the world smoke, comprising about 35\% of men in developed countries and 50\% of men in developing countries. About 250 million women in the world are daily smokers, comprising of about 22\% of women in developed countries and 9\% of women in developing countries\textsuperscript{30}. In addition, many women in South Asia chew tobacco either alone or as Pan, combined with areca nut and spices. The use of ‘smokeless tobacco’ in the form of a buccal ‘quid’ is also very prevalent in other, usually lower income groups.

At least 15\% of adolescents in the world are estimated daily smokers, with peaks of around 25-35\% or more in Eastern Europe, Latin America the USA and South Africa\textsuperscript{30}.

Tobacco use accounts for 20-30\% of all cases of oral cancer\textsuperscript{44}. There are more than 60 carcinogens present in tobacco smoke and at least 16 carcinogens in unburned tobacco. Carcinogenicity of tobacco chewing is dose-dependent while carcinogenicity of snuffing is less evident\textsuperscript{30}. A significant dose–dependent relationship between tobacco smoking and the risk for oral and oropharyngeal
cancers have consistently been demonstrated worldwide by both prospective and retrospective studies\textsuperscript{45}. The risk of head and neck cancer increases markedly when the duration of the smoking habit is longer than 20 years and the daily frequency is greater than 20 cigarettes\textsuperscript{44}.

In South Africa, one in nine deaths is related to tobacco use, making this a major public health concern\textsuperscript{46}. The highest incidence in the country has been recorded in the Western Cape where one in five deaths is tobacco-related\textsuperscript{47}. Over the past two decades increases of 100\% in mortality rates from lung cancer among coloured men and of 300\% among coloured women have been recorded in the Western Cape\textsuperscript{47}. Reddy and co-workers\textsuperscript{47} found that 34\% of adult South Africans smoked (52\% male, 17\% female), with males smoking more than females in all race groups except coloureds (58\% of men and 59\% of women smoked).

Although the prevalence of tobacco use has declined in some high-income societies, it continues to increase in low- and middle-income societies, especially among young people and women. The prevalence of tobacco use in most countries is highest amongst people of low educational background and among the poor and marginalized people\textsuperscript{48}. Notably though, the study by Kuper and co-workers\textsuperscript{49} found tobacco to be the strongest independent risk factor for oral lesions causing higher cancer death rates in high-income countries (16\%) than in low-income countries (10\%). Cigarette, pipe, cigar and bidi smoking, betel quid chewing (pan), guhtka use and other traditional forms of tobacco have all been implicated as risk factors for oral cancer and oral cancer recurrence. A study on the role of the type of tobacco in oral carcinogenesis found that smokers of black (air-cured) tobacco compared to smokers of blond (flue-cured) tobacco were at a significantly higher risk of developing oral cancer even after allowing for the amount and duration of
smoking\textsuperscript{24,50}.

4.1.2 Alcohol

The main active ingredient in alcoholic beverages is ethanol produced by fermentation of carbohydrates by yeasts. Spirits, such as whiskey, brandy and vodka are produced by distillation of fermented products. Carbohydrate fermentation is incomplete in beer and complete in wine, with resulting alcohol content of 3-8\% and 7-18\% respectively. Consumption of alcoholic beverages such as wine dates back to more than 10 000 years ago. It is believed that beer has existed even longer. In fact, beer appears to have been an important source of nutrients and calories for earlier civilizations. Alcohol was also used for medicinal purposes, as an anodyne and to relieve fatigue\textsuperscript{30}.

Alcohol consumption has long been implicated as one of the traditional risk factors for oral cancer. This association is dose-dependent. A case-control study estimated that the risk of developing oral cancer was approximately 50-fold greater for heavy smokers and drinkers than for those who never smoked and never drank\textsuperscript{42}. The separate effects of tobacco and alcohol consumption have been difficult to differentiate because their combined use is so common. It has however been found that alcohol drinking is an independent risk factor for the development of oral premalignant lesions\textsuperscript{42}. Of interest is a finding that a study of South American local liquors found that locally prepared indigenous beverages, were more likely to contain measurable quantities of toxic contaminants such as nitrosamines, polycyclic aromatic hydrocarbons and aromatic and aliphatic fuel oils than were commercially prepared drinks\textsuperscript{45}.
The actual mechanism whereby the consumption of alcohol increases the risk of oral cancer remains unclear. Several mechanisms have been postulated:

- Although the bulk of alcohol metabolism occurs in the liver, extrahepatic metabolism has been shown to occur in the oral cavity. This results in the formation of acetaldehyde which is a primary metabolic product of ethanol and is mutagenic\(^42\). Oral microflora, particularly aerobic flora, produce considerable quantities of acetaldehyde during alcohol consumption. Previous studies have concluded that oral streptococci may contribute significantly to the normal individual variation of salivary acetaldehyde levels after alcohol drinking and thereby increase the risk of oral cancer\(^42\).

- Alcohol may act as a solvent that facilitates the passage of carcinogens through cellular membranes\(^31\).

- The cytochrome p450 enzyme, CYP2E1, is induced by ethanol and this has been shown to correlate significantly with the generation of hydroxyethyl radicals and with lipid peroxidation products such as 4-hydroxy-2-nonone (4-HNE) and malondialdehyde (MDA). These DNA-reactive aldehydes in turn form mutagenic exocyclic DNA adducts that have been shown to promote carcinogenesis\(^51\) and may also function to activate carcinogens\(^31,52\).

- Ethanol may alter the intracellular metabolism of target cells, and this may be aggravated by nutritional deficiencies\(^31\).

- Ethanol may cause direct irritation to the area\(^31\).

Despite these hypotheses, pure ethanol by itself has not been proven to be carcinogenic\(^31\).

An interaction between tobacco and alcohol has been reported with evidence that
their combined effect is at least greater than the sum of the two independent effects and probably multiplicative\cite{30,31,53}.

Alcohol abuse is associated with loss or insufficient intake of essential micronutrients\cite{54}. Vitamin C deficiency is a common finding in patients with alcoholic liver disease. Marked tissue depletion of vitamin E (α-tocopherol), a key scavenger of free radicals, is also associated with alcohol abuse. Low levels of β-carotene have been reported in exfoliated oral mucosal cells of heavy consumers of alcohol\cite{55}. The most widely used chemopreventive agents against oral cancers are anti-oxidants and free radical scavengers such as vitamins A, E, C, and β-carotene, derived from foods. Alcohol is thus also responsible for a loss of protective anticancer mechanisms. Alcohol-related cancers may therefore very well represent neoplasias induced and/or promoted by micronutrient deficiencies\cite{30}.

4.1.3 Areca Nut

The areca nut comes from the palm *areca catechu*. It is commonly incorrectly referred to as the betel nut. The betel leaf comes from the vine *Piper betle*. The areca nut is chewed on its own or together with the betel leaf. Occasionally, the betel leaf is chewed on its own. Commonly, the betel quid is chewed. This is composed of the betel leaf smeared with lime that may contain pieces of the areca nut, tobacco or snuff, and many other condiments or sweeteners\cite{5}. Betel quid chewing, with or without the inclusion of tobacco, has long been identified as a major risk factor for oral cancer in older Asian populations\cite{31}. It is a habit practiced by about 600 million people in south-east Asia and the Pacific islands\cite{30}.

The chewing of the areca nut results in the liberation of alkaloids, arecoline being the dominant one. It is a natural cholinergic agonist similar to nicotine. The areca
alkaloids interact with the muscarinic receptors and influences the function of the nervous system, via acetylcholine. This results in stimulation of the salivary, lacrimal, gastric, pancreatic, and intestinal glands and the mucosal cells of the respiratory tract. The heart rate is reduced and the pupils of the eye constrict. The net effect is increased capacity to work with euphoric effects and heightened alertness. Betel quid has been classified as an oral carcinogen in humans by the International Agency for Research on Cancer, with evidence of a dose-response relationship. Its carcinogenicity may be related to the process of endogenous nitrosation and the production of potentially carcinogenic nitrosamines. There have also been reports of the generation of reactive oxygen species in the oral cavity due to auto-oxidation of polyphenols contained in the areca nut and enhanced by the alkaline pH of the slaked lime.

The prevalence of areca nut chewing among Indians in Durban has been shown to be substantially higher in women than in men. A study by van Wyk and co-workers on the areca nut chewing habit and OSCC in South African Indians confirmed an association between areca nut chewing and buccal cancer. They also concluded that elimination of this habit can reduce the risk of oral cancer in these women by 89-91% if all other factors remain the same. Our study has shown that Asian females have the highest ASIR for OSCC among all females and have a LR of 1:217 of developing OSCC. These facts need further investigation to determine whether areca nut chewing is the underlying cause.

4.1.4 Viral Infection

Epstein-Barr virus (EBV) and Human Papillomavirus (HPV) have been implicated in oral and oropharyngeal carcinogenesis. Studies have shown EBV DNA in up to 53%
of oral squamous cell carcinomas\textsuperscript{31}. Llewellyn and co-workers\textsuperscript{31} do however state that further analysis of large samples is necessary to determine whether EBV has a causative role in OSCC or whether its presence is coincidental\textsuperscript{31}. A strong causal role has however been established for EBV in the development of nasopharyngeal carcinoma (NPC). The involvement of EBV in NPC has been postulated since 1966 and confirmed in 1970 when anti-EBV antibodies were observed to be higher in NPC patients than in controls\textsuperscript{56}. Various techniques have been used to detect EBV in EBV-associated neoplasm such as polymerase chain reaction (PCR), Southern blotting, immunohistochemistry, and in situ hybridization (ISH). Among these, only the ISH technique can directly localize EBV DNA or EBER in the nuclei of tumour cells, differentiating it from that in the viral infected lymphocytes in the peripheral vessels\textsuperscript{56}.

Although the overall incidence of head and neck squamous cell carcinoma has been decreasing slowly over the past two decades, epidemiological studies over the same period show a steadily increasing incidence of cancer of the oropharynx and tongue in younger white individuals, both male and female\textsuperscript{34,57,58,59}. In the USA, from 1973 to 2001, the rate of incidence of oropharyngeal cancer rose by 2.1% in men and 3.9% in women aged 20-44 years \textsuperscript{60}. Similar trends have been noted in Stockholm and Finland\textsuperscript{52}. In contrast to the ‘typical’ patient with oral and oropharyngeal cancer, these patients often have not been exposed to the common risk factors, alcohol and/or tobacco, suggesting other risk factors, including oncogenic viruses such as HPV\textsuperscript{52,57,60}. HPVs are epitheliotropic, oncogenic DNA viruses with more than 120 strains already identified. Some 15 of these strains are considered to pose a high risk of inducing neoplastic transformation, with HPV 16 and 18 accounting for the largest percentage of HPV-induced cancers\textsuperscript{61}. 
The HPV viral genome encodes for six non-structural proteins including two viral oncoproteins, namely E6 and E7. These oncoproteins target the p53 and pRB tumour suppressor pathways respectively, rendering these pathways dysfunctional in the majority of HPV related cancers\textsuperscript{60,61}. The expression of p16, a tumour suppressor protein that inhibits cyclin dependant kinase 4A, is upregulated as a consequence of the inactivation of pRb\textsuperscript{62}. Immunohistochemical methods can be used to determine HPV involvement through detection of increased levels of p16 expression, with a very high sensitivity and about 80\% specificity \textsuperscript{63}. However, in situ hybridisation, with a specificity of almost 100\%, is the method of choice for detecting p16 for final confirmation of the presence of HPV\textsuperscript{63}. Several studies have reported on the prevalence of HPV in squamous cell carcinoma of the head and neck\textsuperscript{34,52,58,60,61,64}. High-risk HPV DNA has been consistently detected in 20-72\% of cases of oropharyngeal squamous cell carcinoma\textsuperscript{60}. HPV infection is the most important risk factor in the aetiology of uterine cervical cancer\textsuperscript{61}. The study by Postma and van Heerden\textsuperscript{32} showed that the incidence of OSCC and cervical squamous cell carcinoma in blacks and coloureds, and OSCC in white males correlated significantly over the ten-year period 1986-1995, possibly indicating a common cause. They hypothesized that HPV could be this common aetiological factor.

Current evidence suggests that orogenital contact may be the primary mode by which HPV is transmitted to the upper aerodigestive tract\textsuperscript{34,57,60}. DesMarteau \textsuperscript{65} states that the increase in HPV-positive oropharyngeal cancers could well be an additional but unanticipated burden of the HIV epidemic since many people consider oral sex to be ‘safer sex’ because of the danger of HIV infection. Thus, the admonition to practice ‘safer sex’ seems to have led to an increase in the prevalence of oral sex, even though the true rate of HIV transmission via oral sex is unknown.
4.1.5 Dietary Factors

Globally, up to forty percent of cancers are attributable to unhealthy diet, lack of physical activity and obesity. Deficiencies in fruits, non-starchy vegetables and foods containing carotenoids, are associated with oral cancer, with 10-15% of oral cancer cases attributable to micronutrient deficiency. The literature suggests that a diet high in fruit and vegetable intake may protect against oral cancer. The beneficial effect of fruits and vegetables has been attributed to several micronutrients, flavinoids, polyphenols and fibres. Their mechanisms of action include antioxidant effects and binding and dilution of carcinogens in the digestive tract. The micronutrients could therefore play an essential role in counteracting the detrimental effects of other carcinogens, such as tobacco, alcohol or betel nut. The study by Marshall and Boyle showed a high frequency of fruit eating was associated with diminished risk of cancer among both males and females, fruit consumption being inversely associated with incidence of oral cancer. More than any specific nutrient, including carotene, vitamin C, fibre, folate, thiamine, riboflavin, niacin, vitamin E and iron, the intake of fruit was found to be consistently associated with decreased incidence of oral cancer.

Of significance to the South African context is that urbanization is an important factor responsible for the alteration of dietary habits. There is a continuous urban influx of rural people in search of livelihood. Food choices among rural populations are simple but natural and based on their own vegetable and animal produce. However, food choices among urban populations are largely driven by cost and convenient availability. Processed foods as opposed to fresh animal and garden products are
ready to eat, easily available and less expensive. Other factors influencing the average urban diet include meals away from home, mass media advertising, social events and peer pressure\textsuperscript{30}.

Beverages are an important component of our daily diet. Coffee holds second position in consumption among all beverages after water\textsuperscript{67}. Its consumption is associated with a reduced risk of liver, kidney, and to a lesser extent, postmenopausal breast cancers and colorectal cancers\textsuperscript{67}. There is evidence for the anticancer effects of the coffee-specific lipidic diterpenes cafestol and kahweol (C+K), which have been shown to reduce the formation of DNA adducts of several genotoxic carcinogens. C+K may act as blocking agents, by reducing the activation of procarcinogens and/or stimulating multiple phase II detoxifying enzymes. From animal studies, caffeine and coffee polyphenols (chlorogenic acids (CGAs)) also appear to have anticarcinogenic activity\textsuperscript{68}.

Biazevic and co-workers\textsuperscript{69} in Brazil, which is one of the largest producers and consumers of coffee in the world, found, after adjusting for sociodemographic factors, that regular coffee drinking over a long period affords some protection against the risk of oral and oropharyngeal cancer.

4.1.6 Genetic Factors

Since only a few people exposed to potential carcinogens develop cancer, it has been suggested that an intrinsic susceptibility to extrinsic carcinogens may play a role in the aetiology of head and neck cancer. Oral cancers arise through a series of mutations in tumour suppressor and other genes\textsuperscript{31}. About 45% of head and neck squamous cell carcinomas have a mutation at the p53 tumour suppressor gene\textsuperscript{70} making this the single most frequent genetic mutation observed in these
carcinomas. Studies on the association of OSCC susceptibility with various genotypic polymorphisms such as cytochrome P450 (CYP1A1) and glutathione-S-transferase (GSTM1) have demonstrated that patients with such polymorphisms have a genetically higher risk of oral cancer owing to diminished detoxification of carcinogens and reactive oxygen species.

4.1.7 Material deprivation and the link with oral cancer

Low socioeconomic status is believed to be one of the risk factors for oral cancer. However, the data from studies on the association of socioeconomic status and oral cancer are conflicting. Greenberg and co-workers could not demonstrate any association of oral cancer with education or occupation. Social and economic instability, as indicated by joblessness, is more detrimental to the risk of oral cancer than is social disadvantage, including material deprivation. In the study by Hashibe and co-workers, individuals with low income and low education were more likely to chew tobacco, to smoke cigarettes, and to drink alcohol. Furthermore, low income and disadvantaged groups have less access to health services and health education. Some studies have shown a decreased risk of oral cancer associated with higher socioeconomic status, as determined by occupation and higher educational levels. Though this seems to be true in developed countries, paradoxically in less developed countries, higher income seems to increase the risk for oral cancer. It is thus still unclear whether material deprivation is indeed an independent risk factor for cancer in general or for oral and oropharyngeal cancers in particular, or whether it is merely a marker for lifestyles replete with known risk factors and missing protective factors.
Chapter 5

5.1 Conclusion

It is possible that the total ASIR for oral and oropharyngeal cancer has increased in South Africa. The ASIR of oral squamous cell carcinoma for coloured males is higher than that reported by Breytenbach (1979)\(^\text{41}\) whilst the ASIR of oral squamous cell carcinoma for black males (5.823) is also higher than those reported by Altini and Kola (1985)\(^1\).

When compared to the global average of about 6% of oral cancers occurring in young people under the age of 45 years\(^3\), our data reveals that 7.276% and 7.844% of all cases occurred in those below 45 years old, in males and females, respectively. The rate of incidence of oropharyngeal squamous cell carcinoma in those below the age of 45 was 10.9% and 11.45%, for Asian and coloured females, respectively. This may indicate a disturbing trend and warrants further study.
References


