RISK OF ORAL CANCER ASSOCIATED WITH TOBACCO SMOKING AND ALCOHOL CONSUMPTION

- A CASE CONTROL STUDY IN THE WESTERN CAPE, SOUTH AFRICA.

RAKESH CHANDRAN

A mini thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Dental Public Health in the Department of Community Dentistry, University of the Western Cape.

Supervisor:
Professor Neil Myburgh

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Master of Science in Dental Public Health, Department of Community Dentistry, University of the Western Cape.

ABSTRACT

Tobacco and alcohol consumption are well-established, high-ranking health risk behaviour in developed countries and the developing countries are catching up rapidly. There is very strong evidence in the literature to show that these behaviours feature prominently in the web of causation of many diseases either proximally or distally contributing substantially to global morbidity and mortality. Oral cancer is an important preventable cancer proven to be directly associated with tobacco and alcohol in many overseas studies. The study examines this association in detail for the population of the Western Cape Province in South Africa in order to establish the existence, extent, dose and the duration of use relationship and the possibility of synergistic effect of these two often co-existing risk behaviours in the causation of oral cancer. A hospital based, analytical case control study using histologically confirmed cases originating from a single homogenous population group of the Western Cape was designed. Necessary data on 67 cases were collected from the Cancer Unit of Groote Schuur Hospital in Cape Town and that of 67 controls from other clinics in the same hospital using an interview schedule specifically prepared and tested in the same hospital. The cases and controls were individually matched for age, gender and ethnicity. The statistical analysis of the data shows that: (1) There is strong relationship between oral cancer and smoking (Odds Ratio 4.63, 1.74–12.30 95% C.I) and alcohol use (Odds Ratio 7.21, 3.07-16.93 C.I); (2) The risk increases by six fold when the duration of use is more than 35 years in case of tobacco and eleven fold with more than 30 years of alcohol use; (3) The quantity of tobacco (>10 cigarettes/day) and alcohol (>500 grams/week) increases the risk of oral cancer by two fold and twenty four fold respectively; (4) Very few people in the study were able to quit the habit and thus the existence of risk reduction with cessation of the habit could not be proven statistically; (5) Statistically significant synergism exists among the people who indulge in smoking and alcohol use (Odds Ratio 9.61, 2.909-31.73 C.I). The findings of the study strongly support the efforts of the South African government to implement the tobacco legislation strictly and its campaign for responsible drinking. Concerted efforts though media campaign and education among the adolescents are strongly recommended. This study did not examine the effect of poor oral hygiene in the development of oral cancer and further research is suggested.

DECLARATION

I declare that 'Risk of oral cancer associated with tobacco smoking and alcohol consumption- A case control study in the Western Cape, South Africa' is my own work, that it has not been submitted before for any degree or examination in any other university, and that all the sources I have used or quoted have been indicted and acknowledged as complete references.

Rakesh Chandran **November 2003**

Signed.....

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GLOSSARY

Oral Cancer. In the context of this study oral cancer refers to oral squamous cell carcinoma, which accounts for more than 90% of all oral malignant lesions. It refers to intra oral cancer, which excludes cancers of the lip, nasopharynx and salivary glands.

Risk Factor. Risk factor is an agent, attribute or behaviour that is directly part of the causal chain of the disease.

Smoking. Smoking is inhaling and exhaling the fumes of burning plant materials, especially tobacco, from a cigarette, cigar or pipe.

Tobacco. Tobacco is a preparation of the dried leaves of the numerous species of Nicotiana. Common tobacco is Nicotiana tabacum, native to South America, Mexico and the West Indies. Wild tobacco is Nicotiana rustica, the species cultivated by the Indians of North America and presently cultivated in Turkey, India and several European countries.

Cigar. Cigar is a cylindrical roll of tobacco for smoking, consisting of cut tobacco filler formed in a binder leaf and with a wrapper leaf rolled spirally around the bunch.

Cigarette. Cigarette is paper- wrapped roll of finely cut tobacco for smoking; modern cigarette tobacco is usually of a milder type than cigar tobacco.

Snuff. Snuff is the powdered preparation of tobacco used by the inhalation or by dipping that is, rubbing on the teeth and gums.

Gutkha or Paan masala. Gutkha is a dry complex mixture, with or without tobacco, of areca nut, catechu, lime, cardamom, flavourings and sweetening agents.

Heavy Drinking. Heavy drinking is usually defined as drinking over 14 units per week for women and 21 units per week for men; a unit is approximately one small glass of wine or sherry, a single measure of spirits or about 300ml of standard beer.

Incidence. Incidence rate is defined as "the number of new cases occuring in a defined population during a specified period of time".

Odds Ratio. In the context of this study an odds ratio expresses the risk of developing oral cancer associated with any specific factor. Values larger than 1.0 indicate increased risk; values less than 1.0 represent a decreased risk or protective effect. Values are usually statistically adjusted to reduce the influence of other risk factors associated with the disease.

Pack Year. 1 pack-year= smoke equivalent to 1 pack of cigarettes per day per year, e.g. 40 pack-years could be 1 pack a day for 40 years, or 2 packs a day for 20 years, etc.

CHAPTER 1

INTRODUCTION

Improvement in the living conditions combined with the innovations in the field of medicine, introduced demographic transition across the globe during the 20th century starting from the more affluent to the less affluent societies. Substantial improvement in life expectancy, population explosion and dramatic changes in life style, driven by technology and trends occurred during this transition. The disease profile of populations changed from that of predominantly communicable diseases to that of non-communicable diseases, cancers, violence and injury and mental disorders. This change, termed the 'epidemiological transition', is attributed mainly to the increase in the geriatric population and the fallout of technological advancement that resulted in the modern way of life. In addition to several notable benefits, the modern lifestyle introduced a new physical and psychosocial environment, where people are exposed to innumerable new and different health risk factors. The risk factors changed the leading causes of mortality and burden of disease in developed countries to ischemic heart disease, cerebro-vascular disease and cancer. A similar pattern is seen among affluent communities within developing countries, resulting in a combined disease profile of communicable and non-communicable diseases (double burden). Even though the HIV/AIDS, which increases the prevalence of some of the cancers, is regarded as the major health problem of South Africa today, cancer and other communicable diseases are increasing rapidly to the levels of developed nations.

The cancer of the trachea, bronchus and lung together is ranked 9th among the leading causes of mortality in the world (WHO, 1999). Jointly all cancers, usually classified according to site and tissue of origin, are a growing health problem in developed and developing countries. Cancer accounts for 7.2 million (13.4%) of all deaths and 80.4 million (5.8%) of the burden of disease measured in Disability Adjusted Life Years annually (WHO, 1999). Cancer of the lung, stomach, colon, breast, uterine cervix, liver, lymphatic system and oral cavity are more common and incidence is dependent on geographic, socio-economic, ethnic and gender factors.

More and more research related to cancer is conducted in various fields of science such as genetics, molecular biology, clinical medicine, pharmacology, clinical and diagnostic radiology and epidemiology. Major part of epidemiologic studies focus on the risk factors associated with various types of cancers. In addition to the genetic predisposition, several carcinogens including radiant energy and ever increasing natural and manufactured chemicals and biological agents are identified in the etiology of cancer. Research on the etiology of cancer is essential for the development of treatment and preventive interventions. The first step in the process is the

establishment of the relation between exposure to carcinogen and the cancer. The patho-physiology of the agent and its interaction at cellular and molecular level leading to carcinogenesis completes the etiological study. Detailed studies of risk-exposure, including its strength, dose-relation, circumstances of exposure and social, behavioral or economic factors leading to the exposure, are important in developing primary prevention strategies against cancer.

The World Health Report 2002: 'Reducing Risk, Promoting Healthy life' (WHO, 2002) is based on a global study of 38 well-known risk-to-health factors. The study reveals that 10 major preventable risk factors listed below are directly related to one-third of the morbidity and mortality worldwide.

Table 1.1 Preventable health risk factors in developed and developing countries.

	Developing Countries High mortality	Developing Countries Low mortality	Developed Countries
1	Underweight	*Alcohol Consumption*	*Tobacco Consumption*
2	Unsafe sex	Underweight	High Blood pressure
3	Unsafe water, sanitation & hygiene	High Blood pressure	*Alcohol Consumption*
4	Indoor smoke from solid fuel	*Tobacco Consumption*	High Cholesterol
5	Zinc deficiency	Obesity	Obesity
6	Iron deficiency	High Cholesterol	Low fruit & vegetable intake
7	Vitamin A deficiency	Iron deficiency	Physical inactivity
8	High Blood pressure	Low fruit & vegetable intake	Illicit drugs
9	*Tobacco Consumption*	Indoor smoke from solid fuels	Underweight
10	High Cholesterol	Unsafe water, sanitation & hygiene	Iron deficiency

Tobacco and alcohol consumption is an established health risk in developed countries and a rapidly growing concern in developing countries. Starting from the well-documented tobacco and lung cancer studies, the association between these two co-existing risk factors and several diseases such as ischemic heart disease, cerebro-vascular disease, different types of cancers, obstructive lung disease, low birth weight, motor vehicle accidents, homicide, domestic violence, mental disorders and gastrointestinal diseases is established. Association between these risk factors and oral cancer is demonstrated in many studies conducted inside and outside South Africa and this study based in the Western Cape examines this relationship in more detail.

South Africa is one of the pioneers in anti-tobacco legislation. Stricter implementation and further amendments are expected. Anti-alcohol campaigns, specifically against its abuse, are gaining momentum. Overwhelming evidence of the etiologic relationships between alcohol and tobacco use with oral cancer as well as other diseases, will emphasise the need for efforts and encourage government to pass tighter regulations.

The prevalence of smoking and alcohol use is comparatively high in South Africa, especially in the Western Cape province and oral cancer accounts for 3 to 5 percent of all the cancers among the white and coloured communities in the Cape Peninsula (Muir Grieve, 1967). In spite of this fact, the research on the risk of oral cancer is very limited in South Africa. It will be very useful to quantify the risk of oral cancer among the smokers and alcohol users in its various population groups. It is hoped that this study will help to bridge this gap.

The research problem and the hypothesis were developed with the help of available literature regarding oral cancer, its risk factors and the methodology used. Several studies on this topic were reviewed. A summary of international and national literature that is reviewed for the purpose is presented in the *second chapter*.

The research problem is defined and study design identified based on the facts established in the first and second chapters. The *third chapter* elucidates the research hypothesis and puts forward the research method that is suitable for the study.

The *fourth chapter* deals with the research design and methodology in detail where sampling design, observational design and operational design of the study are discussed.

The *fifth chapter* tabulates the results with brief discussion on the significance of the findings. Finally the *sixth chapter* concludes the thesis with a summary of the main findings and a few recommendations based on the study.

CHAPTER 2

THE LITERATURE REVIEW

"There is tremendous literature on cancer, but what we know for sure about it can be printed on a calling card" - August Bier [1861-1949]

This chapter examines the academic context in which the hypothesis is developed. The review will focus briefly on cancer in general and oral cancer in more detail. The literature on the risk factors such as smoking and alcohol-use is also reviewed. The purpose of this study is to examine the association between the two major risk factors - smoking and alcohol use. The first section in this chapter looks at the demographic details of this form of cancer. In the second section, a brief note is made on all the risk factors of oral cancer. The last section looks into the epidemiologic studies on tobacco and alcohol consumption individually and in combination.

In the context of this study, oral cancer refers to squamous cell carcinoma and excludes cancers of the lip, nasopharynx and salivary glands (intra oral cancer). Most of the literature on oral cancer refers to squamous cell carcinoma, as it is the most common malignant neoplasm of the oral cavity.

In this study, a risk factor is anything that increases a person's chance of getting a disease such as cancer. Different cancers have different risk factors. Unprotected exposure to strong sunlight is a risk factor for skin cancer, and a diet high in fat and low in fruits and vegetables is a risk factor for colorectal cancer. Scientists have found certain risk factors that make a person more likely to develop oral cavity and oropharyngeal cancer. Some people with oral cavity or oropharyngeal cancer do not have any known risk factors, and others with several risk factors never develop the disease. Even if a patient does have exposure to one or more risk factors for oral cavity and oropharyngeal cancer, it is impossible to know for sure how much that risk factor contributed to the causing the cancer.

AGE, GENDER AND ETHNICITY OF ORAL CANCER

The demographics of those who develop oral cancer have been consistent for some time. While the majority of people are over the age of 40 at the time of diagnosis, it does occur in lower age groups. In the series of 9775 cases of oral cancer reviewed by Krolls and Hoffman (1976), about 32 percent of the patients were in the seventh decade of life, while the vast majority, nearly 87 percent, were between the ages of 40 and 80 years. Oral cancer is rare in the third and fourth decades of life. (Cancer Research Campaign, 1993). The exact causes of the development of oral cancer at younger ages have not been elucidated by research yet, but there are some possible

links to young men who use "smokeless" chewing or spit tobacco. Promoted as a safer alternative to smoking, it has in actuality, not proven to be any safer to those who use it.

From a gender perspective, for decades the oral cancer affected 6 men for every woman. That ratio has now become 2 men to each woman. Again, while published studies do not exist to draw finite conclusions, we will probably find that this increase is due to lifestyle changes, primarily the increased number of women smokers over the last few decades.

The social and cultural variations among ethnic groups strongly influence variation in the incidence of oral cancer. The tobacco and alcohol consumption among black South Africans has been on the increase during the last few decades (Yach and Townshend, 1988). More research needs to be done on the influence of ethnicity on oral cancer in sub- Saharan Africa. In the United States, extremely high incidence and mortality rates were observed among black Americans compared to white Americans (American Cancer Society, 1997).

THE RISK FACTORS ASSOCIATED WITH ORAL CANCER

Tobacco and alcohol contain chemical carcinogens, but they can also be considered lifestyle factors, since we have some control over them. The International Agency for Research on Cancer (1986) has stated that there is sufficient evidence to show that tobacco is carcinogenic, though the precise role of alcohol remains to be established (Wyk, 1982). Besides these, there are physical factors such as exposure to ultraviolet radiation. It is a causative agent of the cancers of the lip, as well as other skin cancers. The incidence of cancer of the vermilion of the lip has declined over the last few decades due to the increased awareness of the damaging effects of prolonged exposure to sunlight, and the use of sunscreens for protection. Another physical factor is exposure to x-rays. Radiographs regularly taken during examinations, and at the dental office, are safe, but radiation exposure is cumulative over the lifetime. It is implicated in several head and neck cancers.

Biological factors, which include viruses and fungi, are found in association with oral cancers. The human papilloma virus, particularly HPV16 and 18, is implicated in some oral cancers. There are about 80 strains of HPV, most of them considered harmless. But 1% of those infected, have the HPV16 strain, which is a causative agent in cervical cancer, and now it is linked to oral cancer as well. Human Papilloma viruses may induce p53 gene mutation, which frequently occurs in oral cancer. Lichen Planus, an inflammatory disease of oral soft tissues is also shown to be associated with oral cancer.

Very few studies examine the familial and genetic predisposition to oral cancer. Families tend to have the same occupation and invariably the same smoking and drinking habits exposing them to the same environmental factors making it difficult to differentiate. The association, if any, has minimal significance.

Much of the tobacco in the world is consumed without combustion, by being placed into contact with mucous membranes, through which the nicotine is absorbed. Betel quid is prepared from areca nut, cured or sun dried, and chopped. These pieces are placed on a leaf of Piper betel vine. Slaked lime is an essential ingredient. The lime is prepared by baking limestone where available: near coasts this is more often from seashells or snail shells. The habit of chewing betel quid is found extensively in Asia, especially in India and Sri Lanka. The quid is held in the oral sulcus. White patches may develop where the quid is held, which shows high risk of malignant change. Betel or areca nut chewing may also cause oral sub-mucous fibrosis – a pre malignant condition. An estimated 200 million people around the world practice this habit (CRC, 1993). The longer the quid is placed in the mouth, the higher the risk and if chewing is combined with smoking tobacco, then the risk is even higher. Gutkha is a form of areca (betel) nut to which chewing tobacco and sugar has been added.

Other risk factors to cancer include occupational exposure to a growing number of chemical and biological carcinogens, dietary exposure to alkaloids, preservatives etc., dietary and other lifestyle related behaviors. A diet low in fruits and vegetables could be a risk factor, and conversely, high intake of such foods may have a protective effect against many types of cancers. The debate on the importance of socio-economic status in health and disease is also relevant here. Even though it is a complex variable very difficult to analyze a recent study by Hobdell et al (2003) established a positive relation with poor socio-economic status and oral cancer. In many instances, the exposure and carcinogenesis is dose related. In a study that examined dose-response relationships, it was found that risks of oral cancer increased with years of use to about fifty-fold for snuff users after fifty or more years of use (Winn, 2001).

THE RISK OF TOBACCO CONSUMPTION

"A cigarette is the only legally available consumer product that kills through normal use." (WHO, 2003).

Tobacco use in all its forms is number one in the list of risk factors for the development of cancer and many other diseases. At least 75% of those diagnosed with cancer are tobacco users. When smoking is combined with heavy use of alcohol, the risk is significantly increased, as these two acts synergistically.

Tobacco will soon become the leading cause of death worldwide, causing more deaths than HIV, maternal mortality, automobile accidents, homicide and suicide combined. (CDC, 1999) Currently tobacco causes around 13,500 deaths per day worldwide (WHO, 2003). Seventy five percent of all cases of oral cancer can be attributed to the consumption of tobacco (Hille et al, 1996). In general, the risk of developing a tobacco-related cancer depends on the intensity of the habit as

determined by the duration of the smoking habit, number of cigarettes smoked per day, tar content of the cigarette, and the depth of inhalation.

The evidence supporting the causative role of tobacco smoking in oral cancer is strong and is based on epidemiological and experimental evidence. Epidemiologically there is a strong association between the occurrence of oral cancer and smoking and the risk of contracting the disease is higher in heavy smokers and in those who have smoked for a longer time. The risk diminishes in time for those who quit the habit. It is also shown that the 5-year survival rate after diagnosis of oral cancer is very much higher in non-smokers than in smokers (Colgate, 1999).

The cigar smokers are seven to ten times more likely to develop oral cancer than non-smokers (Winn, 2001). In large cohort studies, pipe smokers had 2.0 to 3.5 fold increased risk of developing oral cancer compared to persons who did not smoke (Winn, 2001). Even though the prevalence of pipe smoking is declining, more and more people are taking up cigarette smoking. In South Africa, an estimated 34 percent of the population smokes (Reddy et al, 1996). The Western Cape province has the second highest smoking rate with 48 percent of the population smoking.

Persons who smoke experience six times the relative risk over non-smokers for the development of malignancy (Mashberg et al). A study in Johannesburg (Pacella-Norman, 2002) based on which this present study is developed, shows an association between smoking and oral and laryngeal cancers. The study focuses on the habits of black South Africans. Oral cancer was about four times more frequent in women with no or only primary education (OR= 4.2 and 3.9), compared to those with secondary or higher education; this difference is not found in men. The same study shows a high odds ratio of 12.5 in men who smoke more than 15gms of tobacco per day.

The risk associated with smoking 33 pack years or less (relative to non smokers) is found to be 1.7 (95% C.I. 1.2, 2.5) in males (Macfarlane et al, 1995). This risk rises to 3.8 (95% C.I. 2.5, 5.8) in those who smoke more than 33 pack years. In females the risk relative to non-smokers was 2.7 (95% C.I. 1.6, 4.7) for those who smoke 18 pack years or less and 6.2 (95% C.I. 3.4, 11.2) for those having smoked more than this. The risk decreases with increasing duration of cessation. The risk is reduced to 70% after quitting between 1 and 9 years when compared to those still smoking.

In a population based case-control study, cigarette smokers experienced the risk of oral cancer two to five times more than that of non-smokers (Blot et al, 1988). The risk increases with the number of cigarettes smoked and the years smoked. Although epidemiological studies consistently report that oral cancer risk declines with the number of years of abstinence from cigarettes, it will take many years before the risk declines to those of non-smokers (Blot et al, 1988).

All forms of tobacco smoking carry the risk of oral cancer and particularly high rates occur when reverse smoking with the lighted end inside the mouth is practiced (Cancer Research Campaign, 1993). Another form of cigarette is 'Bidi'. These are cheap South Asian cigarettes. These are now being imported into the Western countries.

In an effort to reduce smoking, the Tobacco Products Control Amendment Act of 1999 came into effect in South Africa on October 1, 2000 and not only laid down strict parameters limiting where smoking is permissible, but also outlawed the advertising of tobacco products in any form at all, including the sponsorship of sporting or music events.

THE RISK OF ALCOHOL CONSUMPTION

Excessive consumption of alcohol is the second most important risk factor associated with oral cancer. It acts synergistically with tobacco so that the combined damage is more than the sum of the individual relative risks. Alcohol consumption has doubled per capita in the last few decades in many western countries, and this is thought to be the main reason for the rising incidence of oral cancer.

Ogden and Wight (1998) document the role of alcohol in the genesis of oral carcinoma. The authors site three mechanisms by which alcohol can initiate cellular injury leading to carcinoma: the metabolism of ethanol to the highly toxic substance acetaldehyde, increased permeability of cell membranes secondary to the direct solvent effects and disruption of normal cellular DNA repair process. Additional systemic effects related to alcohol consumption may also play a role. Alteration of liver function in chronic alcoholics may decrease the detoxification of substances capable of cellular injury.

Commercial and homemade beer is available in South Africa. Homemade brew is especially popular among the African population group, and this is a major risk factor for oesophageal cancer. (Segal et al, 1988). Sorghum, which is popularly used for beer making, is replaced with maize with sorghum retained only as the fermenting agent. (Segal et al, 1988). The risk of oral cancer is related to the type of alcoholic beverage consumed. A meta-analysis of three case control studies in the U.S, Italy and China (Macfarlane et al, 1995) shows that there is lesser risk of oral cancer with wine than with spirits and beer. But the increased consumption (over 8 drinks per day) of wine increased risk.

People who drink often tend to smoke and vice versa and hence it is quite difficult to assess the importance of alcohol alone as a risk factor. A case control study conducted in Italy (Fioretti et al, 1999) to determine the risk factors in non-smokers revealed alcohol consumption as the major risk factor for oral cancer with an odds ratio about three fold higher in drinkers than in non-drinkers. A direct relation is evident with the duration of the habit with an odds ratio of 3.6 (95% C.I. 1.2-11.2) for those who consumed alcohol for 35 years or longer.

In a meta-analysis of 7,954 cases carried out to examine the risk associated with oral cancer, a relative risk of 2.9 is established for 50gms of alcohol. When the alcohol consumption increased to 100gms, the risk rose steeply to 6 times indicating a significant dose relationship (Bagnardi et al, 2001).

THE RISK OF TOBACCO AND ALCOHOL CO-EXISTANCE

Perhaps the most significant finding on those who drink and smoke heavily is their increased risk of developing oral cancer- 38 fold for men and over 100 fold for women. (Colgate, 1999) There is two-to-four-fold increased risk of developing squamous cell carcinoma in non-drinking smokers, whereas a heavy smoker and drinker have a six-to-fifteen-times increased risk. (Vora et al, 2000).

Most of the studies reviewed were conducted outside South Africa and indicate that two most important risk factors of oral cancer are smoking and alcohol use. Definite correlation with the duration and dose of exposure to these risk factors is established. The hypothesis for this case control study is built on these findings. This study aims to examine these relations in more detail with reference to the Western Cape population.

CHAPTER 3

THE RESEARCH PROBLEM

The importance of oral cancer and smoking and alcohol use as its major risk factors and its dose relation individually and synergistically have been documented in earlier chapters. More clarity on the research problem in the setting of Western Cape province and the development of an hypothesis is done in this chapter.

The incidence of oral cancer varies from place to place. According to the Cancer Research Campaign Fact sheet (1993), there are nearly 2000 new cases and 900 deaths from oral cancer each year in the United Kingdom. In countries like India and Sri Lanka oral cancer is far more frequent. For example, in a hospital in Bombay (India), oral cancer accounted for 40 percent of all forms of cancer (Shafer, 1983). Hille et al (1996) estimated the age-standardized incidence rate (ASIR) of oral cancer in South Africa to be 1,8 percent of all cancers among males. A very high incidence rate of 13,13 percent is seen among coloured men. The incidence of oral cancer increases with age, although the pattern differs markedly in different countries and with different risk factors. There is an increased incidence of oral cancer among the younger generation, which may be attributed to the change in lifestyles of the younger generation exposing them to various carcinogenic substances. Men are more prone to oral cancer than women, probably due to a major extent to the higher indulgence in risk factors such as alcohol and tobacco consumption. However, this trend is changing and in certain high risk areas in South Asia female rates are higher than the male rates (Cancer Research Campaign, 1993), due to betel nut chewing. The sites that are in direct contact with the various risk factors are more likely to be affected. The oral cavity is exposed to the effects of most carcinogenic substances unlike the lungs, which is exposed only to the gaseous substances.

The South African Department of Health has estimated that the smoking of cigarettes costs South Africa about R1 billion per year in medical care, hospitalization, absenteeism, loss of production and decrease in gross national product (Yach, 1995). During 1980 the tobacco industry spent R20 million on advertising in South Africa. Although there is a reduction of smoking among the White population group, smoking among the Coloured and African population groups is on the increase as they become increasingly urbanized. It is clear that the adverse effects of tobacco will be increasingly seen among Africans (Van der Burgh, 1979). In a survey done in 1984 the rural smoking rate was reported as 21.4% compared to an urban prevalence of 32% (Yach and Townshend, 1988).

In the Western Cape population with high prevalence of smoking and alcohol use, research shows that these habits among the younger age groups are increasing and probably accounts for increasing numbers of new cases of oral cancer every year. According to a prevalence study conducted among 11 to 19 year old white high-school children in Cape Town (Prout and Benetar, 1983), the average cigarette consumption by current smokers was 170 cigarettes per month. Of the children surveyed 51% had never smoked, 28% claimed to be ex smokers and 21% were smoking at the time of the survey. Studies combining measurements of carboxyhaemoglobin with questionnaires on smoking status have shown that between 22% and 40% of people claiming to be ex-smokers are indeed still smoking (Sillet et al, 1978) In a survey conducted (Strebel et al, 1989) in three townships in Cape Town, the strongest determinant of smoking is gender. African women and girls smoke at very low levels compared to men who take up the habit in their early teens. This correlates with the very low incidence rate of oral cancer among black women of 1.7 percent of all cancers (Hille et al, 1996) in the Western Cape.

The etiological study on oral cancer is valuable in South Africa for following reasons:

- Even though much less than that of cervix, lung and breast cancer, the prevalence of oral cancer is relatively high.
- Oral cancer has one of the lowest five-year survival rates among cancers.
- Its relationship with several risk factors is established in studies elsewhere and its relevance in South Africa is not very clear.
- Tobacco and alcohol use are two major risk factors and its use in South Africa is relatively high, around 34% of the population. (Reddy et al, 1996).
- It is considered as one of the preventable cancers.
- Epidemiological research on oral cancer is very limited in South Africa.

The list of carcinogens that induces different types of cancer is growing regularly and it includes sunlight, radiations, chemicals and viruses. Understanding the circumstances and behaviour that exposes people to such carcinogens is important in preventing the cancer. For example, the incidence of the cancer of oral cavity has reduced dramatically in some South Asian countries after a successful campaign against the habit of chewing tobacco and betel nut (Gupta, 1991,1992).

In summary, several risk factors related to cancer have been studied extensively and the smoking habit tops the list. A definite relationship between smoking and several cancers is clearly established across the world. Alcohol use is perhaps the second most important risk factor, also causing several other disease conditions. A study in South Africa and several other studies in other countries have shown smoking and alcohol use as the most important risk factors for the development of oral cancer (Pacella-Norman, 2002). Since the demographic characteristics, habits and environment vary from communities to communities, it is important that such studies

are conducted in various settings to establish the relationship with the risk factor and disease of interest.

THE PURPOSE OF THE STUDY

A study to measure the risk of smoking and alcohol use towards the development of oral cancer in the Western Cape region will enable us to compare the results with similar studies done in other geographic settings. In addition, the study aims to examine the dose relationship and synergistic effects of these two risk factors.

THE OBJECTIVES OF THE STUDY

The hypotheses that this study intends to test are:

- **A strong relation exits between smoking and oral cancer in the Western Cape**
- **A strong relation exists between alcohol use and oral cancer in the Western Cape**
- **The relative risk of these two risk factors increases with high dose exposure and decreases with cessation of the habit.**
- **There is a synergistic effect when both the risk factors are present.**

The estimation of odds ratio of oral cancer in those exposed to the risk factor over those not exposed is the preferred method to test the hypothesis.

THE RESEARCH FRAMEWORK

A prospective cohort studies is best suited to investigate the etiologic risk factors in which a sample population without the disease is followed up for long period to measure the ratio of people developing disease with and without exposure. Since it is difficult to conduct such studies, especially for relatively rare conditions, the retrospective case control method, is used as a more suitable alternative. Effectively, this method tests the past exposure, from 40 to 50 years back in case of oral cancer, using matched case (with disease) and controls (without disease) simulating a cohort from the past. This is the method commonly used in cancer studies where the time lag between the exposure and development of disease is long.

Most of the cancer patients from the Western Cape and neighboring provinces are seen at the oncology clinic in Groote Schuur Hospital, a state funded academic hospital. Reasonably large numbers of oral cancer patients are registered in this clinic, which is used as the universe of 'cases'. Matching controls are selected from the same hospital population. Necessary data for the study can be collected in a 3 to 4 months period to test the hypothesis using statistical methods. The next chapter deals with the study design in detail.

CHAPTER 4

RESEARCH DESIGN AND METHODOLOGY

The main research problem of the study is to examine the risk of developing oral cancer due to smoking and alcohol use and its relation to the quantity and the duration of the exposure. This requires the comparison of the occurrence and non-occurrence of the disease in a defined population with exposure, to that of an 'equivalent' population without exposure to the risk factors. In an experiment to prove or disprove this hypothesis, two groups of subjects with and without exposure of measured dose of a risk factor can be followed up for a specific period and the development or non-development of the disease determined. Definitely, such experiments on human subjects are unethical.

Similar natural experiments can be designed by following up two population groups in a non-experimental exposure and non-exposure situation. After observing these two groups for a defined period, depending on the natural history of the disease (specifically the known or estimated time lag between exposure to risk factor and disease development), the presence or absence of disease in two groups is compared. Epidemiologically, such prospective cohort study is the ideal and accurate method to investigate risk factors. The cohort design tends to be rather expensive since several hundreds of people have to be enrolled and studied with regard to exposure and outcome for long period. It is not suitable to study diseases of long induction period such as oral cancer mainly due to attrition of the subjects, difficulty in maintaining the momentum of the study and the cost.

Case control study is an attractive, cheaper and quicker alternative, demanding fewer resources especially for relatively rare diseases with long induction period. In case control study design, a cohort of population is retrospectively reconstituted and starts with the subjects with disease rather than the healthy subjects in a prospective cohort study. The control subjects without disease are selected in such a way that each case is compared as far as possible with similar subjects. It is done using the technique of 'matching' the variable such as age, gender and psycho-socio-economic and environmental factors. Matching is mostly dependant on the exposure(s) studied and known and possible confounding variables. They also provide the possibility of investigating a wide range of risk factors together. One serious disadvantage of the case control study is the difficulty of selecting perfectly matching controls in relation to the cases to mimic the experimental or prospective study situation. Overmatching of coexisting risk factors is a drawback, which leads to masking of the existing association.

It is essential to design the case control study carefully considering all the important steps and possible bias to produce a reliable result. These steps includes:

- Clearly stated study hypothesis
- Definition and selection of cases with strict inclusion and exclusion criteria
- Decision to include all available (prevalent) cases or only new (incident) cases
- Definition and selection of controls with strict inclusion and exclusion criteria
- Definition of the source of control to represent the population from which cases are drawn.
- Ratio of the case to control, 1:1 is optimal and up to 1:4 justified.
- Proper sampling scheme of the control
- Definition of matching variables
- Decision to use individual or frequency matching method.
- Definition of exposure and strength and duration of exposure

In a case control study, necessary demographic and exposure data is collected using interview or other observation methods. Design, training of interviewer/observer, piloting and coding of the data collection tool is an important aspect of the study to avoid observer and responder bias.

THE STUDY DESIGN

The overall design used in this study is 'hospital based, individually matched analytical case control study using prevalent cases originating from a single homogenous population group'. The cases and controls are selected from the same hospital and the study population can then be defined as potential 'hospital users'. This is to overcome the possible selection bias of population-based controls.

The source of the cases is Groote Schuur Hospital, an academic hospital situated in Cape Town and managed by the provincial administration of the Western Cape Province. The cases consisted of patients attending the Head and Neck cancer clinic and the controls were selected from those attending the diabetic, dermatology, geriatric, lupus, arthritis, neurology, surgery, urology, breast, neurosurgery, dental, orthopaedics, hands, gynaecology, endocrinology, thyroid, genetics, medical, renal and lipid clinics in the same hospital.

THE SAMPLING DESIGN

Sample Size Estimation

The sample size of the cases needed for the study is estimated using the statistical software Epi Info 2000. According to Reddy et al (1996) 34% of the adult population smokes in South Africa. Accordingly, this figure of 34% is used as the percentage exposure among the control (not ill) group. The power of the study is set at 80% and the confidence interval 95%. The cases are matched to the controls at 1:1 ratio. The estimated odds ratio is 3. A total of 134 subjects are

interviewed, 67 cases and 67 controls matched for age gender and the status of residence in the Western Cape province.

THE SELECTION CRITERIA FOR CASES AND CONTROLS

The selection criteria for the cases

All patients diagnosed with squamous cell carcinoma between August 1997 and August 2002 formed the study population for the cases. Eligible cases were those with cancer diagnosis of ICD-9 codes 140-149 (oral cavity), but excluding ICD-9 140 (lip), ICD-9 142 (salivary glands) and ICD-9 147 (nasopharynx). Patients who attended the Head & Neck Clinic during the period were chosen as a convenient sample considering the inclusion and exclusion criteria. New and follow up patients were included. The subjects with a diagnosis of squamous cell carcinoma that was confirmed histopathologically are used. All subjects were above the age of 35, born in the Western Cape and a resident of the Western Cape for a period of not less than 20 years.

The selection criteria for the controls

The controls were matched to the cases for age and gender and ethnicity. All subjects were healthy, did not suffer from cancer in any location, born and current resident of the Western Cape province for a minimum period of 20 years. A convenient sample of controls was selected from different clinics that satisfied matching criteria of the cases.

The exclusion criteria for the cases and controls.

Very ill patients and those who refused to participate in the study were excluded for ethical reasons. All other oral cancers except for squamous cell carcinoma were excluded. Patients from outside the Western Cape region were also excluded.

THE OBSERVATIONAL DESIGN

The questionnaire for the interview of the cases and controls.

A structured questionnaire based on a standard one used in a similar study in Johannesburg was used (Pacella-Norman et al, 2002). The questionnaire made reference to (see Appendix 1):

- Demographic variables including age, gender, ethnicity, place of birth, duration of stay at the present residence, occupation and level of education.
- Questions related to tobacco consumption: Whether the subject is a smoker, ex-smoker or had never smoked. If the subject is a smoker or an ex-smoker, the type and the amount of tobacco consumed per day were recorded. The types of tobacco mentioned in the questionnaire are cigarettes, hand rolled cigarettes and pipes. The ages at which the subject started smoking and stopped were included. This was included to estimate the

total number of years the person smoked. The use of snuff was also recorded in a similar way.

- Questions related to alcohol consumption: Questions regarding the type of alcohol consumed and the quantity. Beer, spirits and wine were the types of alcohol to choose from. The subject was questioned on the quantity of alcohol consumed and the data was entered as bottles, glasses etc. A pamphlet was designed with the pictures of various types of alcohol consumed, in various bottle and glass sizes. (see Appendix 3).

The test of a sound measurement tool (questionnaire) is its validity, reliability and practicality (Kothari, 1990). The validity of the questionnaire (ability to measure what is supposed to be measured) is satisfactory except for the recall bias involved in some of the questions, more importantly that of controls. Data on the issues of past usage of tobacco and alcohol and the time of stopping the habit may not be accurate. All possible precautions were made to improve reliability (the ability to produce consistent results) by reducing response and observer bias. The questions were asked in a uniform format in the vernacular of the subjects by the same person. Even though attention was given to the place of interview, attitude of the interviewer and the atmosphere of interview, such bias could not be completely excluded in an interview. The economy, convenience and interpretability are three measures of practicality. The choice of case control method, optimum sample size, use of only relevant questions, selection of hospital based cases and controls, clarity of questions and use of pictures to measure alcohol intake are some of the steps taken in this study to improve practicality. The questionnaire was piloted in the same hospital to test its practicality and usability.

THE OPERATIONAL DESIGN

The operational design included the following activities:

- Preparation of the questionnaire and piloting
- Discussion with colleagues, supervisors and clinic staff for guidance
- Obtaining permission to conduct the study
- Obtaining funds to the conduct the study,
- Appointment and training of a research assistant for data collection
- Obtaining approval from the Higher Degrees Committee of the University
- Preparation of necessary stationery for data collection
- Scheduling the data collection with the staff of Head and Neck Clinic

The consent, permission and ethical clearance were obtained by July 2002. Data collection commenced in August 2002 and ended in December 2002. The cases were interviewed on Fridays when the Combined Head and Neck operated. The controls were interviewed on the days when the respective clinics operated.

DATA COLLECTION AND ANALYSIS.

Data were collected on the questionnaire according to the operational plan. The data were cleaned, collated and coded properly before being captured into a specially prepared Excel Spreadsheet. Accuracy of data capture was rechecked. Few items in the questionnaire such as quantity of smoking and alcohol use, age of subjects, etc., were categorized for the purpose of statistical analysis.

The analysis of tobacco consumption

Tobacco consumption was categorised as current smoker, past smoker and non-smoker. Those who had not smoked for the past five years were considered as past smokers. One hand rolled cigarette was regarded as equivalent to 2 cigarettes and one cigar equivalent to four cigarettes. The smokers were categorised according to their cigarette consumption of up to 10 cigarettes a day and more than 10 cigarettes per day.

The analysis of alcohol consumption

The difficulty of assessing the role of alcohol on oral cancer stems from the fact that it mostly occurs together with the smoking habit. Another difficulty in assessing the role of alcohol was the accurate measurement of intake (e.g. variation in quantity, type and alcohol concentration). Data on alcohol ingestion was based on a highly subjective estimate provided by the patient (Ogden, 1998). In addition it was difficult to obtain reliable information from the patient. Some may 'binge drink' and others have a 'high daily intake'.

The conversion of alcohol to 'Ethanol Equivalent'

In alcohol use, several variables such as the amount, frequency, container and the types of beverages consumed create difficulty in estimating the dose. For purpose of uniformity the values used by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) is used (Pattison and Kaufman, 1982). The percentages of ethanol present in the various brands of alcoholic beverages available in South Africa vary. The percentages of some of the brands available are given in the Appendix 2. For the purpose of this study the ethanol content of beer is 4.5%, wine 12% and hard liquor is 43%; these assumptions coincide with the NIAAA studies of alcohol consumption. Alcohol consumption is evaluated in grams of alcohol/week. The ethanol equivalent of the alcohol consumed is obtained from the following formula:

Grams of alcohol =ml of ethanol x 0.8

A spreadsheet was prepared in Microsoft Excel to compute the total alcohol content of the various beverages (Appendix 2). Separate tables for the conversion of beer, wine and spirits consumed to milliliters of ethanol content are also attached as Appendix 6,7 and 8.

The cases and the controls were matched and the data was transferred into Statistical Package for Social Scientists (SPSS). The frequency tables, McNemar Tests and binary logistic regression analysis are done using the statistical software.

THE LEGAL AND ETHICAL STATEMENT

The protocol was submitted for approval to the ethical committees at the University of the Western Cape and the University of Cape Town (see Appendix 9). Permission to conduct the interview was obtained from the Medical Superintendent, Head of Radiation Oncology Division and Chairman of the combined head and Neck clinic, Groote Schuur Hospital, Cape Town (see Appendix 10).

The participants were given the right to refuse or withdraw at any stage of the interview. The confidentiality and anonymity of the collected data was ensured. The feedback will be given to the subjects involved in the study and the Head and Neck Clinic and the University of Cape Town.

The study does not involve any experimental situation and the issue of consent for interview is strictly adhered. A copy of the consent form is attached as Appendix 2.

THE LIMITATIONS OF THE STUDY DESIGN

Use of individual matching and hospital based cases and controls in itself is a limitation of the study design but practicality is given preference here. The case and control samples were not selected randomly since the available number of patients was small, but inclusion and exclusion criteria were observed. It was difficult to construct a sampling framework especially for the controls. The effect of this selection bias was considered in the interpretation of the result.

CHAPTER 5

THE PRESENTATION AND DISCUSSION OF THE FINDINGS

The results of the data analysis are tabulated and the findings briefly discussed in this chapter. The adequacy and appropriateness of case-control matching is discussed first. The demographic detail of case and control is presented in the next section. The analysis of the risk factors begins with the tabulation of the frequency of various variables on which data were collected. This is followed with the analysis of the association of risk factors to oral cancer to test the hypothesis. For the purpose of substantiating the inferences, two different statistical methods of analysis are used to estimate the relationship, namely the McNemar Test and the Logistic Regression Analysis. The final section looks at the risk of combined exposure to smoking and alcohol use.

MATCHING OF THE CASES AND CONTROLS.

The matching of the cases and controls is an important aspect of this study for increasing the validity of the inferences by controlling the confounding factors. Age, gender, occupation, socioeconomic status, place of birth and ethnicity are the possible confounding factors in the study. Since all the subjects included in this study were born in the Western Cape, the influence

Table 4.1: Age matching for cases and controls

AGE MATCHING FOR CASES AND CONTROLS				
	Males		Females	
	Cases	Controls	Cases	Controls
SD	9.97	10.03	14.30	14.53
Mean	57.87	57.92	58.55	58.65
Min	40	38	34	33
Max	80	80	87	88

of the 'place of birth' as a confounding factor is nullified. The subjects were selected from the same hospital, thus decreasing the influence of socio-economic status. From the 90 cases and 101 controls interviewed, 67 cases were selected and were matched for age, sex and ethnicity to the controls. There were 47 males and 20 females in each category. The statistics for the matching for age are shown in Table 4.1. The mean age of the males is 58 and that of the females 59. The very small difference in the standard deviation of the cases and the controls for the males and the females shows that they were adequately matched. The subjects were matched for ethnicity as indicated in Table 4.2. Since the cases and the controls were

individually matched to a large extent, the findings of the study can be attributed to the risk factors under consideration.

THE DEMOGRAPHIC FEATURES OF THE SUBJECTS

Most of the patients interviewed were from the coloured population group. They constitute a half the sample size in the study (Table 4.2). The subjects were mostly English and Afrikaans speaking (Table 4.3). Few interviews were conducted in Xhosa, but the subjects were not included as they were from the Eastern Cape and thus did not meet the selection criteria. Most of the subjects had lived in the Western Cape for at least 40 years (Table 4.4)

Table 4.2: Ethnic distribution of case and controls

ETHNINC DISTRIBUTION OF THE CASES AND CONTROLS		
	Case (%)	Control (%)
African	8 (12%)	2 (3%)
Coloured	39 (58%)	43 (64%)
Indian	1 (2%)	4 (6%)
White	19 (28)	18 (27%)
Total	67 (100%)	67 (100%)

Table 4.3 Language distribution of the cases and controls

LANGUAGE DISTRIBUTION		
	Case (%)	Control (%)
Afrikaans	24 (36%)	9 (13%)
English	43 (64%)	58 (87%)
Total	67 (100%)	67 (100%)

Table 4.4: Residential status of case and control

RESIDING IN THE WESTERN CAPE		
	Case (%)	Control (%)
20—39 years	15 (22%)	11 (16%)
40- 59 years	34 (51%)	36 (54%)
60- 79 years	17 (25%)	18 (27%)
80- 99 years	1 (1%)	2 (3%)
Total	67 (100%)	67 (100%)

THE ANATOMICAL DISTRIBUTION OF THE LESION

The location of cancer in the mouth or the 'site of lesion' was recorded from the case sheets of the case group. In some instances the tumour had spread to adjacent areas and it is documented as site 2 (Table 4.5). The most common site for squamous cell carcinoma according to the study is the tongue followed by the floor of the mouth. Twenty-six cases suffered from oral cancer of the tongue.

Table 4.5: Location of oral cancer lesions among the cases

Anatomical site	SITE 1 Frequency (%)	SITE 2 Frequency (%)
Buccal Mucosa	4 (6%)	
Floor of the mouth	15 (22%)	
Gingiva	4 (6%)	1 (9%)
Oropharynx	4 (6%)	
Others	3 (5%)	
Palate	9 (13%)	1 (9%)
Tongue	26 (39%)	5 (45%)
Tonsils	2 (3%)	4 (37%)
Total	67 (100%)	11 (100%)

THE ANALYSIS OF THE RISK FACTORS

The risk factor analysis is done using the McNamer Test and Linear Logistic regression (Martin Bland, 1987) for each of the risk factors studied. Only two of the subjects claimed to have used snuff and the period of use was diminutive. The subject used snuff for a few days as a remedy for a blocked nose. The data was insufficient to conduct analysis on the association between snuff and oral cancer. It was difficult to record the socio-economic status adequately due to non-disclosure of information and resulting missing data made it unsuitable for analysis.

THE FREQUENCY OF THE RISK FACTORS

The frequency of various variable related to the risk factors studied is tabulated in Table 4.6 below and this analysis was done for cases and controls separately. Other important findings related to smoking were:

- Among the men 88.3% smoked compared to 60% amongst women.
- The median age at which the cases and controls started smoking was 18 and 19 for men and women respectively.

- The average number of years the cases and controls smoked were 37.7 and 29.2 respectively.
- The three types of tobacco consumed were cigarettes, hand rolled cigarettes and pipes.
- The difference between medians of the number of cigarettes smoked among the cases and the control group was significant (p =0.008).
- Six persons in the case group smoked hand rolled cigarettes compared to none in the control group. Five persons in the case group smoked pipe compared to none in the control group.

Table 4.6 Frequency of the variables related to the risk factors

Variable (N=67)	Cases		Controls	
Non smokers	7	(10.45%)	20	(29.85%)
Past Smokers	13	(19.40%)	18	(26.87%)
Current Smokers	47	(70.15%)	29	(43.28%)
<35 years of smoking	28	(41.79%)	31	(46.27%)
>35 years of smoking	32	(47.76%)	16	(23.88%)
<10 cigarettes/day	24	(35.82%)	26	(38.81%)
>10 cigarettes/day	31	(46.27%)	21	(31.34%)
Do not consume alcohol	12	(17.91%)	41	(61.19%)
Consume alcohol in the past	17	(25.37%)	8	(11.94%)
Consume alcohol currently	38	(56.72%)	18	(26.87%)
<30 years of alcohol consumption	23	(34.33%)	16	(23.88%)
>30years of alcohol consumption	32	(47.76%)	10	(14.93%)
<100 grams of beer/week	18	(26.87%)	6	(8.96%)
>100 grams of beer/week	21	(31.34%)	7	(10.45%)
<300 grams of wine/week	14	(20.90%)	11	(16.42%)
>300 grams of wine/week	27	(40.30%)	2	(2.99%)
<300 grams of spirits/week	7	(10.45%)	8	(11.94%)
>300 grams of spirits/week	15	(22.39%)	5	(7.46%)
<500 units of alcohol/week	24	(35.82%)	20	(29.85%)
>500 units of alcohol/week	32	(47.76%)	5	(7.46%)

Some other important findings related alcohol use in addition to that given in Table 4.6 are listed below:

- Among the men, 71.3% used alcohol compared to 35% of the women.

- The average age at which the cases started consuming alcohol was 21 compared to 24 in the controls.
- The average age at which the cases drank heavily was 29 while the age at which the controls drank heavily was 33.
- Of the 55 original alcohol users 20 stopped using alcohol in the case group and out of the 26 original alcohol users 11 controls stopped using alcohol.
- The two matched groups differed with respect to the number of years of alcohol usage. The cases drank on average 32.1 years compared to 27.5 years in the controls.
- The 39 beer drinkers in the cases group drank on average 247.4ml weekly. The 13 beer drinkers in the control group drank on average 115.6ml.
- The 41 wine drinkers in the case group drank on average 819.6ml weekly. The 13 wine drinkers in the control group drank on average 323.1 ml weekly.
- The 22 spirit drinkers in the case group drank on average 668.6ml and the 13 spirit drinkers in the controls drank 447ml weekly. The two averages were significantly different.
- When all three types of alcohol were considered together, 55 users of alcohol in the case group used in total 851.5ml alcohol weekly compared to 481.5ml in the control group.

The Table 4.7 and 4.8 presents the gender and age distribution of subjects in the study. It shows that smoking and drinking is more prevalent among males.

Table 4.7 Gender and age distribution of the smokers

	Non smoker		Past Smoker		Current Smoker		Total
Male	11	(11.7%)	24	(25.5%)	59	(62.8%)	94
Female	16	(40.0%)	7	(17.5%)	17	(42.5%)	40
Age 30-59	17	(21.8%)	15	(19.2%)	46	(59.0%)	78
Age 60-89	10	(17.9%)	16	(28.6%)	30	(53.6%)	56

Table 4.8 Gender and age distribution of the alcohol users.

	Non Alcohol user		Past Alcohol user		Current Alcohol user		Total
Male	27	(28.7%)	20	(21.3%)	47	(50.0%)	94
Female	26	(65.0%)	5	(12.5%)	9	(22.5%)	40
Age 30-59	27	(34.6%)	15	(19.2%)	36	(46.2%)	78
Age 60-89	26	(46.4%)	10	(17.9%)	20	(35.7%)	56

The risk behaviour appears to decrease with increasing age in the population studied.

The Table 4.9 analyses the co-existence of the risk factors. Almost one-third of the subjects are currently consuming alcohol and tobacco and there are more current smokers than current

alcohol users. Another finding is the relatively small number of alcohol users among the non-smokers.

Table 4.9 Cross tabulation of smoking and alcohol use

	Non Alcohol user	Past Alcohol user	Current Alcohol user	TOTAL
Non smoker	**21 (15.67%)**	1 (0.74%)	5 (3.73)	27
Past smoker	12 (8.9%)	12 (8.9%)	7 (5.2%)	31
Current smoker	20 (14.92%)	12 (8.9%)	**44 (32.83%)**	76
TOTAL	53	25	56	134

TOBACCO CONSUMPTION AND ORAL CANCER

Regression analysis is generally used in case control studies to test the relationship. However, the McNemar test is recommended for the individually matched studies. The McNemar Test was done as explained in Appendix 4, where smoking was categorized into current smokers (Y), past smokers (P) and those who never smoked or non-smokers (N). Past smokers were those who had not smoked for the past five years. The test indicated a statistically significant relationship between smoking and oral cancer with a p-value of 0.01.

The results of logistic regression analysis (Table 4.10) confirmed the result presented above. The odds of developing oral cancer was 2-fold (95% CI 0.675-6.311) higher for past smokers and 4-fold (95% CI 1.743 12.304) higher for current smokers compared to non-smokers. The odds of developing oral cancer was 6-fold (95% CI 2.001-16.318) higher for a person who smoked more than 35 years and 2-fold (95% CI 0.995-6.082) higher for a person who smoked more than ten cigarettes per day when compared to non-smokers.

Table 4.10: Logistic Regression analysis of Tobacco Consumption

	Case/Control	P value	Odds ratio	95% C.I.	
				Lower	Upper
TOBACCO CONSUMPTION ANALYSIS					
Non smoker	7/20	.005	1		
Past smoker	13/18	.204	2.06	.67	6.31
Current smoker	47/29	.002	**4.63**	1.74	12.30

	Case/Control	P value	Odds ratio	95% C.I.	
				Lower	Upper
THE AGE AT WHICH THE SUBJECTS STARTED SMOKING					
Non smokers	7/20	.026	1		
10-16	30/23	.011	**3.72**	1.34	10.31
>16	30/24	.014	**3.57**	1.29	9.84
THE NUMBER OF YEARS THE SUBLECTS SMOKED					
Non Smoker	7/20	.004	1		
1-35 years	28/31	.063	2.58	.94	7.02
>35 years	32/16	.001	**5.71**	2.00	16.31
CIGARETTES SMOKED PER DAY					
Non Cig Smoker	12/20	.140	1		
<10 cigarettes/day	22/26	.351	1.54	.62	3.80
>10 cigarettes/day	38/21	.051	**2.46**	.99	6.08
TOTAL TOBACCO CONSUMED PER DAY					
Non Smoker	7/20	.005	1		
1-10 units/day	22/26	.093	2.42	.86	6.77
>10 units/day	38/21	.001	**5.17**	1.87	14.22

ALCOHOL CONSUMPTION AND ORAL CANCER

The findings for the association of alcohol consumption and oral cancer are presented in a similar manner to that of tobacco consumption analysis. Alcohol consumption is categorized into current drinkers (Y), past drinkers (P) and those who had never drunk (N). Past drinkers were those who had not drunk for the past five years. The McNemar test was done as presented in Appendix 4, and showed a strong relationship between alcohol use and oral cancer (p=0.0001). The results of the logistic regression analysis (Table 4.11) confirmed the above findings. The odds for developing oral cancer was 7-fold higher for past drinkers and current drinkers compared to non-drinkers. A 5-fold increase in risk was noted for those who drank up to 30 years and 10-fold increase for those who drank more than 30 years compared to non-drinkers. The dose relation of the risk behavior was established since odds ratio for the development of oral cancer for those who drink more than 500ml of alcohol was 24.4.

Table 4.11: Logistic Regression Analysis for Alcohol Consumption

	Case/Control	P value	Odds ratio	95.0% C.I.	
				Lower	Upper
ALCOHOL CONSUMPTION PROFILE					
Non drinker	12/41	.000	1		
Past drinker	17/8	.000	**7.26**	2.52	20.92
Current drinker	38/18	.000	**7.21**	3.07	16.93
THE AGE AT WHICH THE SUBJECTS STARTED DRINKING ALCOHOL					
Non drinker	12/41	.000	1		
1-10	33/14	.000	**8.05**	3.28	19.74
11-54	22/12	.000	**6.26**	2.41	16.24
THE NUMBER OF YEARS THE SUBJECTS DRANK ALCOHOL					
Non drinker	12/41	.000	1		
1-30 years	23/16	.001	**4.91**	1.98	12.15
30-70 years	32/10	.000	**10.93**	4.19	28.50
BEER CONSUMPTION PER WEEK					
Non Beer drinker	28/54	.000	1		
1-100 grams	18/6	.001	**5.79**	2.06	16.21
>100 grams	21/7	.000	**5.79**	2.19	15.25
WINE CONSUMPTION PER WEEK					
Non Wine drinker	26/54	.000	1		
1-300 grams	14/11	.038	**2.64**	1.05	6.61
>300 grams	27/2	.000	**28.03**	6.19	126.95
SPIRIT CONSUMPTION PER WEEK					
Non Spirit drinker	45/54	.068	1		
1-300 grams	7/8	.930	1.05	.35	3.11
>300 grams	15/5	.021	**3.60**	1.21	10.67
COMBINED ALCOHOL CONSUMPTION PER WEEK					
Non drinker	12/41	.000	1		
1-500 grams	24/20	.001	**4.58**	1.88	11.16
>500 grams	32/5	.000	**24.41**	7.71	77.31

Table 4.12: Logistic Regression Analysis for Alcohol Consumption (cont.)

	Case/Control	P value	Odds ratio	95.0% C.I.	
				Lower	Upper
TYPES OF ALCOHOL CONSUMED					
Non drinker	12/41	.000	1		
1 type	21/13	.000	**5.52**	2.14	14.19
2 types	22/12	.000	**6.26**	2.41	16.24
3 types	12/1	.001	**40.99**	4.82	348.07
> 1 type	34/13	.000	**8.93**	3.60	22.12

Analysis was done to examine the risk associated with consuming more than one type of alcohol simultaneously (Table 4.12). It is noted that 34 cases and 13 controls consumed more than one type of alcohol. The risk of developing oral cancer was 8.9 (95% CI 3.608-22.129) fold higher for those who consumed more than one type of alcohol compared to non-drinkers.

THE EFFECT OF COMBINED TOBACCO AND ALCOHOL CONSUMPTION

People who smoke usually drink and vice versa. The McNemar test and the Logistic regression analyses (Table 4.13) were done to test the association. The McNemar test was significant as explained in the appendix 4, with a P-value of 0.001.

Table 4.13: Logistic Regression Analysis for Alcohol and Smoking Combined

	Case /Control	P value	Odds ratio	95.0% C.I.	
				Lower	Upper
COMBINED ANALYSIS OF TOBACCO AND ALCOHOL CONSUMPTION					
Non smoker non drinker	4/17	.000	1		
Non drinker but smoker	8/24	.614	1.42	.367	5.473
Non smoker but drinker	3/3	.143	4.25	.613	29.449
Smoker and drinker	52/23	.000	**9.61**	2.909	31.730

The Table 4.13 clearly indicated the synergistic effect of two risk factors in the causation of oral cancer. The odds ratio for 'smoker and drinker' in the above Table was 9.6 and it is higher than the sum of odds ratios of the 'non-drinker but smoker' and 'non-smoker but drinker', which was 5.7. This result concurred with the earlier finding of the regression analysis for smoking (odds

ratio 4.6) and alcohol consumption (odds ratio 7.2), where all smokers and drinkers were included in the analysis.

An important conclusion and a surprise finding of this study was the relatively higher odds ratio for alcohol use compared to smoking. This is true for the population of Western Cape, for the research methodology and sample size used. The findings were consistent for both the statistical methods employed. The strong association between the number of years of alcohol and tobacco use and the occurrence of oral cancer was demonstrated in this study. Usually people consume more than one type of alcohol simultaneously either individually or mixed. The risk was higher in these people compared with those who consumed just one type of alcohol. Further specific studies need to be done to confirm this interesting finding. The combined effect of smoking and drinking on oral cancer is a highly significant finding.

The findings satisfactorily realize the objectives of the study and all the hypotheses are proven to be true except for the effect of cessation of risk factors. The cessation of risk factor suggested risk reduction but the finding was statistically insignificant.

LIMITATIONS OF THE STUDY

The sample size was inadequate to conduct the analysis of certain variables and its categories such as use of snuff, hand rolled cigarette and pipe smokers. Oral hygiene is considered as an important risk factor of oral cancer and remains a confounding factor in this study and it was not addressed in the design or analysis of the study. Other similar less important factors include socio-economic determinants and literacy, which was not considered in the design. The effect of the withdrawal of alcohol and tobacco consumption was analysed but was not statistically significant probably because there were only a few subjects in this category.

CHAPTER 6

THE CONCLUSIONS AND RECOMMENDATIONS

The objectives of the study to test the hypothesis that a strong relation exists between smoking and alcohol use in the development of oral cancer in the Western Cape area are proved positively using two different statistical techniques. Other hypotheses that risk of oral cancer due to exposure to tobacco and alcohol is proportional to the dose of exposure and the synergistic effect of these risk factors on oral cancer are also true. Even though risk reduction after cessation of the habit was shown, the result was statistically not significant in this study.

The dose response relationship between tobacco smoking and oral cancer demonstrated in a number of studies reviewed earlier was reproduced in this case-control study of patients with a histologically confirmed diagnosis of oral cancer. The increase in risk according to the number of cigarettes smoked per day would seem to support a causal relationship between smoking and oral cancer. Among the cases, 90% were smokers compared with 70% of controls and the risk of developing oral cancer for smokers was 2 times higher for the past smokers and 5 times for current smokers compared to non-smokers.

Most tobacco consumed in South Africa is in the form of manufactured cigarettes. More than 70% of the smokers in the study used manufactured cigarettes as opposed to 4% who rolled their own and 3% who smoked pipe. It was noticed that none of the controls smoked hand rolled cigarettes or pipes. It implies that the main source of tobacco consumption in the Western Cape is manufactured cigarettes. Snuff use is not popular in the Western Cape and has not been mentioned in the literature. The risk associated with the type of tobacco consumed could not be investigated, as the percentage of tobacco consumed in forms other than manufactured cigarettes was very low.

An independent role for alcohol consumption and the synergism between drinking and tobacco smoking, which has been demonstrated in several investigations of oral cancer risk is replicated. Among the cases 82.1% drank while only 38.8% of the controls drank some form of alcohol. The chances of having oral cancer are more definite for alcoholics than smokers in this population group.

Wine is manufactured in the Western Cape and proved to be the major type of alcohol in use (40.30% of the subjects) and 38.80% consumed beer while only 26.12% consumed spirits. Among the cases 49.23% consumed more than one type of alcohol compared to only 19.40 % among the controls. When the quantity of alcohol was combined for the three forms of alcohol in use, namely beer, wine and spirits based on the ethanol content it is found that the odds for developing oral cancer was 7 fold higher for past drinkers and current drinkers compared with non-drinkers.

Other significant findings of the study included:

1. Consumption of more than four 750ml cans of commercially available beer per week causes a five-fold risk in developing oral cancer compared to a person who never drinks beer.
2. Consumption of more than 3 and a half litres of commercially available wine per week increases the chances of developing oral cancer by 28 fold compared to a person who does not drink wine.
3. Consumption of more than a bottle (750ml) of commercially available spirits per week increases the chances of developing oral cancer by 3 fold compared to a person who does not drink spirits.
4. People who consume more than one type of alcoholic beverage are more likely to develop oral cancer.
5. A person who smokes and drinks alcohol at the same time is 9 times more likely to develop oral cancer compared to a person who does not drink nor smoke.

POLICY RECOMMENDATIONS

The findings of this study support and provide added motive for the implementation of the initiative of 'International Treaty for Tobacco Control' of the World Health Organization. South Africa is one among the member countries that adopted the world's first Public Health Treaty, 'The WHO Framework Convention on Tobacco Control'. This country is in the forefront of anti-tobacco regulation and boldly passed the world's first comprehensive tobacco control regulation. Strict implementation of the said act is recommended at national, provincial and local level.

The definite association of oral cancer with alcohol or alcohol-mix use and combined alcohol and tobacco use is proven and the list of diseases caused by alcohol is on the increase. Informal initiatives for the responsible use of alcohol are gaining momentum in South Africa. Sports sponsorship of alcohol manufacturing companies is considered undesirable nowadays. A comprehensive Alcohol Control regulation similar to that of Tobacco Control is recommended.

More intensive anti-tobacco and anti-alcohol campaigns are essential to check the rising morbidity and mortality associated with these risk behaviours.

Both tobacco and alcohol use are addict forming habits. Initiation of the habit must be avoided. Health education targeting school and college students must be intensified. If possible regular health education classes starting from junior primary students are recommended.

RECOMMENDATIONS FOR FURTHER RESEARCH

The effect of poor oral hygiene on oral cancer is not clear in this study and it is a co-existing risk factor among alcohol and tobacco users. A study to identify the relative risk of poor oral hygiene status alone among the alcohol and tobacco users is recommended. The association of socio-economic status and oral cancer needs to be investigated considering its relationship with the habit of smoking and alcohol use. The educational status and oral cancer is another interesting field of study.

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APPENDIX

Appendix 1: QUESTIONNAIRE AND CONSENT FORM

QUESTIONNAIRE Record No ☐☐☐

Case ☐ Control ☐ Case/Control No ☐☐

Name ☐ Phone No ☐☐☐☐☐☐☐☐☐☐

Sex Male ☐ Female ☐ Phone No ☐☐☐☐☐☐☐☐☐☐

Population Group Black ☐ Coloured ☐ Indian ☐ White ☐

Preferred language English ☐ Afrikaans ☐ Xhosa ☐ Other ☐

Date of birth Day ☐☐ Month ☐☐ Year ☐☐☐☐ **OR** Age ☐☐

Diagnosis ☐

Site 1 ☐ Hospital No ☐☐☐☐☐☐☐☐☐☐

Site 2 ☐ RT Folder No ☐☐☐☐☐☐☐☐☐☐

Have you undergone any biopsy? Yes ☐ No ☐

Were you born in the Western Cape? Yes ☐ No ☐

How long have you lived in the Western Cape? ☐☐ Years

What is your usual or past occupation? ☐

How many years of education do you have? ☐☐ Years

None ☐ Lower Primary ☐ Higher Primary ☐ Sec. S ☐ High. S ☐ University ☐

Have you ever smoked cigarettes or a pipe regularly? Yes ☐ In the past ☐ Never ☐

In the past, how many would you usually smoke in a day? (Approximately)

Cigarettes ☐☐ Hand rolled cigarettes ☐☐ Pipes ☐☐

How old were you when you first started smoking regularly? ☐☐ Years

How old were you when you were smoking the most? ☐☐ Years

If you have stopped how old were you when you stopped? ☐☐ Years

Have you ever used snuff Yes ☐ No ☐

In the past, how often would you use snuff each day? ☐☐ Times per day

Did you ever consume alcohol? Yes ☐ In the past ☐ Never ☐

How old were you when you first started drinking regularly? ☐☐ Years

How old were you when you were drinking the most? ☐☐ Years

If you have stopped how old were you when you stopped? ☐☐ Years

About how much wine, beer or spirits do/did you drink on average each week? (E.g. 3 glasses of maize beer would be 3 e)

BEER				SPIRITS		WINE	OTHER
Maize	Sorghum Cartoon	Homemade	Commercial	Homemade (Gavini)	Commercial		

EPIDEMIOLOGY STUDY CONSENT FORM

GROOTE SCHUUR HOSPITAL, OBSERVATORY, CAPE TOWN

My name is .....

I am a student/ an interviewer at the University of the Western Cape.
We would like you to take part in a study to identify the factors that cause disease. The information gained would add to our current knowledge of diseases and thus would help to implement preventive strategies to improve the health and welfare of the community.

I am asking you to spend 10-15 minutes answering questions about yourself and your work and your habits.

Do you have any questions so far?
You may refuse to answer any questions if you choose. All answers will be treated confidentially. If you decline to participate or if you decline to answer some questions this will not affect your treatment in any way.

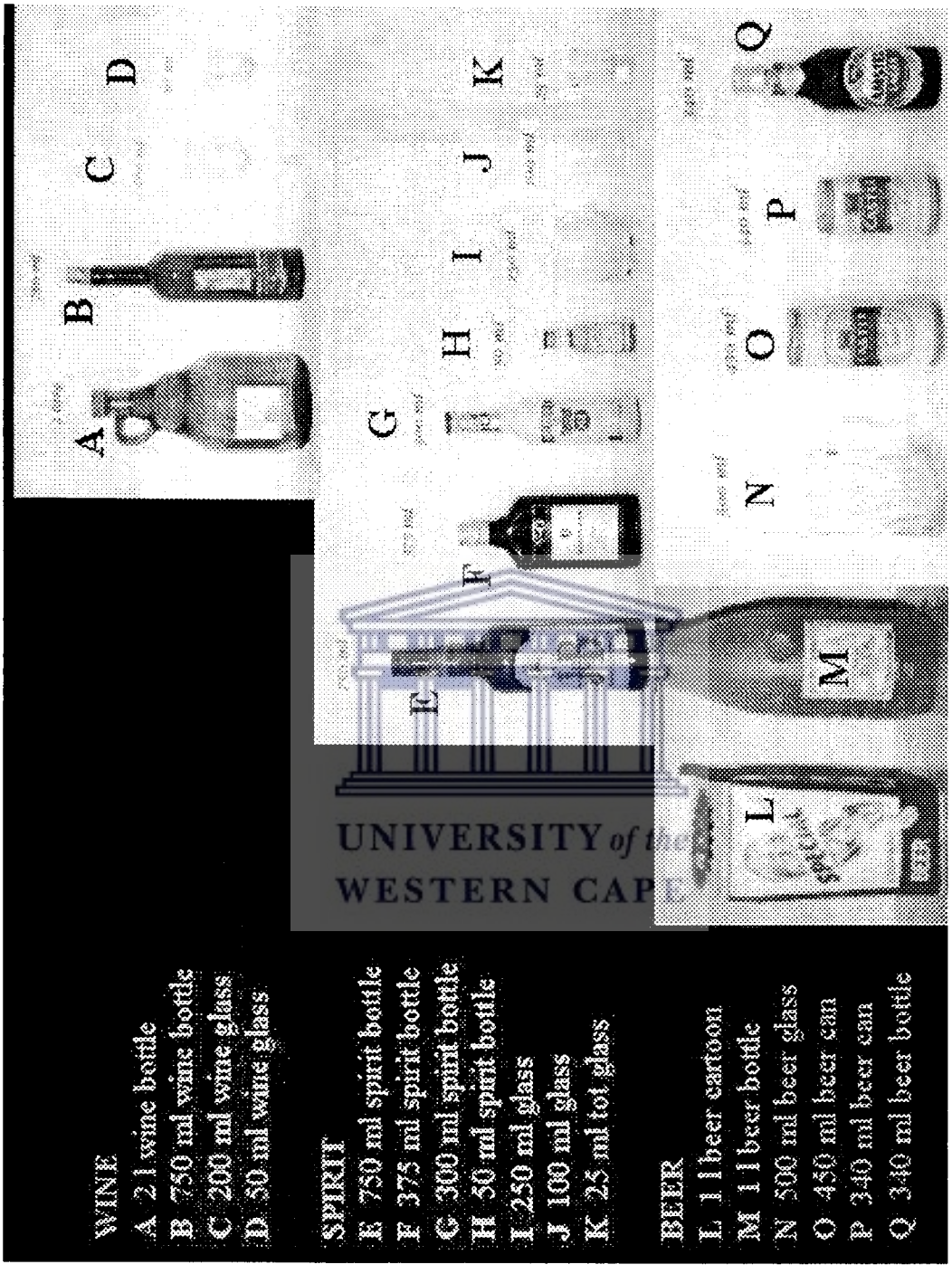
This is a consent form. It says in writing what I have just told you. Please sign and date it here to show that you have understood what I have told you and that you willingly agree to answer questions.

Signature..... Date.....

Signature of witness..... Date.....

(In case verbal consent is given)

Appendix 2: PAMPHLET FOR IDENTIFICATION OF ALCOHOL



Appendix 3: CONVERSION OF ALCOHOL TO ETHANOL EQUIVALENT

Ethanol content of some alcoholic beverages

Wine list		
Drostdy Hof White	9%	volume
Drostdy Hof Red	12%	Volume
Cabernet Sauvignon	13%	volume
Culenborg Late Harvest White	11%	volume

Beer List		
Hansa Pilsner	4.5%	volume
Heineken	5%	volume
Castle Lager	5%	volume
Amstel Lager	5%	volume

Spirits List		
Bertrams Brandy	43%	volume
Richelieu Brandy	43%	volume
Oude Meester Brandy	43%	volume
Johnnie Walker Whisky	43%	volume
Bells	43%	volume

Ciders and Others		
Amarula	17%	volume
Smirnoff ICE	5.6%	volume
Naughty by nature	5%	volume

Spreadsheet for conversion of quantity of alcohol (% volume) consumed to ml of ethanol equivalent

CODE	ML	%	ETHANOL	CODE	TIMES	TOTAL
A	2000	11	220	A		0
B	750	11	82.5	B		0
C	200	11	22	C		0
D	50	11	5.5	D		0
E	750	43	322.5	E		0
F	375	43	161.25	F		0
G	300	1	3	G		0
H	50	43	21.5	H		0
I	250	43	21.5	I		0
J	100	43	21.5	J		0
K	25	43	10.75	K		0
L	1000	1	10	L		0
M	1000	1	10	M		0
N	500	4.5	22.5	N		0
O	450	4.5	20.25	O		0
P	340	4.5	15.3	P		0
Q	340	4.5	15.3	Q		0
BEER	750	4.5	33.75			0
BEER	1000	4.5	45			0
					SUM	0

Table for conversion of quantity of beer (4.5% volume) consumed to ml of ethanol equivalent

4.5	ml	1l	2l	3l	4l	5l	6l	7l	8l	9l	10l
50	2.3	47.3	92.3	137.3	182.3	227.3	272.3	317.3	362.3	407.3	452.3
100	4.5	49.5	94.5	139.5	184.5	229.5	274.5	319.5	364.5	409.5	454.5
150	6.8	51.8	96.8	141.8	186.8	231.8	276.8	321.8	366.8	411.8	456.8
200	9.0	54.0	99.0	144.0	189.0	234.0	279.0	324.0	369.0	414.0	459.0
250	11.3	56.3	101.3	146.3	191.3	236.3	281.3	326.3	371.3	416.3	461.3
300	13.5	58.5	103.5	148.5	193.5	238.5	283.5	328.5	373.5	418.5	463.5
350	15.8	60.8	105.8	150.8	195.8	240.8	285.8	330.8	375.8	420.8	465.8
400	18.0	63.0	108.0	153.0	198.0	243.0	288.0	333.0	378.0	423.0	468.0
450	20.3	65.3	110.3	155.3	200.3	245.3	290.3	335.3	380.3	425.3	470.3
500	22.5	67.5	112.5	157.5	202.5	247.5	292.5	337.5	382.5	427.5	472.5
550	24.8	69.8	114.8	159.8	204.8	249.8	294.8	339.8	384.8	429.8	474.8
600	27.0	72.0	117.0	162.0	207.0	252.0	297.0	342.0	387.0	432.0	477.0
650	29.3	74.3	119.3	164.3	209.3	254.3	299.3	344.3	389.3	434.3	479.3
700	31.5	76.5	121.5	166.5	211.5	256.5	301.5	346.5	391.5	436.5	481.5
750	33.8	78.8	123.8	168.8	213.8	258.8	303.8	348.8	393.8	438.8	483.8
800	36.0	81.0	126.0	171.0	216.0	261.0	306.0	351.0	396.0	441.0	486.0
850	38.3	83.3	128.3	173.3	218.3	263.3	308.3	353.3	398.3	443.3	488.3
900	40.5	85.5	130.5	175.5	220.5	265.5	310.5	355.5	400.5	445.5	490.5
950	42.8	87.8	132.8	177.8	222.8	267.8	312.8	357.8	402.8	447.8	492.8
1000	45.0	90.0	135.0	180.0	225.0	270.0	315.0	360.0	405.0	450.0	495.0

Table for conversion of quantity of wine (11% volume) consumed to ml of ethanol equivalent

1l	ml	1l	2l	3l	4l	5l	6l	7l	8l	9l	10l
50	5.5	115.5	225.5	335.5	445.5	555.5	665.5	775.5	885.5	995.5	1105.5
100	11.0	121.0	231.0	341.0	451.0	561.0	671.0	781.0	891.0	1001.0	1111.0
150	16.5	126.5	236.5	346.5	456.5	566.5	676.5	786.5	896.5	1006.5	1116.5
200	22.0	132.0	242.0	352.0	462.0	572.0	682.0	792.0	902.0	1012.0	1122.0
250	27.5	137.5	247.5	357.5	467.5	577.5	687.5	797.5	907.5	1017.5	1127.5
300	33.0	143.0	253.0	363.0	473.0	583.0	693.0	803.0	913.0	1023.0	1133.0
350	38.5	148.5	258.5	368.5	478.5	588.5	698.5	808.5	918.5	1028.5	1138.5
400	44.0	154.0	264.0	374.0	484.0	594.0	704.0	814.0	924.0	1034.0	1144.0
450	49.5	159.5	269.5	379.5	489.5	599.5	709.5	819.5	929.5	1039.5	1149.5
500	55.0	165.0	275.0	385.0	495.0	605.0	715.0	825.0	935.0	1045.0	1155.0
550	60.5	170.5	280.5	390.5	500.5	610.5	720.5	830.5	940.5	1050.5	1160.5
600	66.0	176.0	286.0	396.0	506.0	616.0	726.0	836.0	946.0	1056.0	1166.0
650	71.5	181.5	291.5	401.5	511.5	621.5	731.5	841.5	951.5	1061.5	1171.5
700	77.0	187.0	297.0	407.0	517.0	627.0	737.0	847.0	957.0	1067.0	1177.0
750	82.5	192.5	302.5	412.5	522.5	632.5	742.5	852.5	962.5	1072.5	1182.5
800	88.0	198.0	308.0	418.0	528.0	638.0	748.0	858.0	968.0	1078.0	1188.0
850	93.5	203.5	313.5	423.5	533.5	643.5	753.5	863.5	973.5	1083.5	1193.5
900	99.0	209.0	319.0	429.0	539.0	649.0	759.0	869.0	979.0	1089.0	1199.0
950	104.5	214.5	324.5	434.5	544.5	654.5	764.5	874.5	984.5	1094.5	1204.5
1000	110.0	220.0	330.0	440.0	550.0	660.0	770.0	880.0	990.0	1100.0	1210.0

Table for conversion of quantity of spirit (43% volume) consumed to ml of ethanol equivalent

43	ml	1l	2l	3l	4l	5l	6l	7l	8l	9l	10l
50	21.5	451.5	881.5	1311.5	1741.5	2171.5	2601.5	3031.5	3461.5	3891.5	4321.5
100	43.0	473.0	903.0	1333.0	1763.0	2193.0	2623.0	3053.0	3483.0	3913.0	4343.0
150	64.5	494.5	924.5	1354.5	1784.5	2214.5	2644.5	3074.5	3504.5	3934.5	4364.5
200	86.0	516.0	946.0	1376.0	1806.0	2236.0	2666.0	3096.0	3526.0	3956.0	4386.0
250	107.5	537.5	967.5	1397.5	1827.5	2257.5	2687.5	3117.5	3547.5	3977.5	4407.5
300	129.0	559.0	989.0	1419.0	1849.0	2279.0	2709.0	3139.0	3569.0	3999.0	4429.0
350	150.5	580.5	1010.5	1440.5	1870.5	2300.5	2730.5	3160.5	3590.5	4020.5	4450.5
400	172.0	602.0	1032.0	1462.0	1892.0	2322.0	2752.0	3182.0	3612.0	4042.0	4472.0
450	193.5	623.5	1053.5	1483.5	1913.5	2343.5	2773.5	3203.5	3633.5	4063.5	4493.5
500	215.0	645.0	1075.0	1505.0	1935.0	2365.0	2795.0	3225.0	3655.0	4085.0	4515.0
550	236.5	666.5	1096.5	1526.5	1956.5	2386.5	2816.5	3246.5	3676.5	4106.5	4536.5
600	258.0	688.0	1118.0	1548.0	1978.0	2408.0	2838.0	3268.0	3698.0	4128.0	4558.0
650	279.5	709.5	1139.5	1569.5	1999.5	2429.5	2859.5	3289.5	3719.5	4149.5	4579.5
700	301.0	731.0	1161.0	1591.0	2021.0	2451.0	2881.0	3311.0	3741.0	4171.0	4601.0
750	322.5	752.5	1182.5	1612.5	2042.5	2472.5	2902.5	3332.5	3762.5	4192.5	4622.5
800	344.0	774.0	1204.0	1634.0	2064.0	2494.0	2924.0	3354.0	3784.0	4214.0	4644.0
850	365.5	795.5	1225.5	1655.5	2085.5	2515.5	2945.5	3375.5	3805.5	4235.5	4665.5
900	387.0	817.0	1247.0	1677.0	2107.0	2537.0	2967.0	3397.0	3827.0	4257.0	4687.0
950	408.5	838.5	1268.5	1698.5	2128.5	2558.5	2988.5	3418.5	3848.5	4278.5	4708.5
1000	430.0	860.0	1290.0	1720.0	2150.0	2580.0	3010.0	3440.0	3870.0	4300.0	4730.0

Appendix 4: EXPLANATION OF THE McNEMAR TESTS

McNEMAR TEST FOR TOBACCO CONSUMPTION

Smoking was categorized into current smokers (Y), past smokers (P) and those that never smoked or non- smokers (N). Past smokers were those who did not smoke for the past five years. The McNemar tests were done as seen in table 4.11.

Because of the individual matching of cases and controls, the unit of the analysis is the matched pair, rather than the individual subjects. Each frequency in the table represents the number of pairs. The 27 (4+12+11) pairs below the diagonal are significant. In each pair, the case counterpart smoked while the control either did not smoke or stopped smoking. In each pair it is seen that the controls are better off. Taking the frequencies above and below the diagonal it is clear that in 27 pairs, the case members smoked more than the control members and in 8 pairs the controls smoked more than the cases. The finding is significant (p=0.01).

McNemar Test for Smoking - Three states N, P and Y into consideration

		Controls			
		N	P	Y	Grand total
Cases	N	4	3	0	7
	P	4	4	5	13
	Y	12	11	24	47
Grand total		20	18	29	67

McNEMAR TEST FOR ALCOHOL CONSUMPTION

The findings for the association of alcohol consumption and oral cancer are presented similar to that of tobacco consumption analysis. Alcohol consumption is categorized into current drinkers (Y), past drinkers (P) and those who never drank (N). Past drinkers are those who did not drink for the past five years. The McNemar test is done as seen in the table below. Taking the frequencies above and below the diagonal it is clear that in 40 pairs the case members used alcohol more than the control members and in 8 pairs the controls consumed alcohol more than the pairs. The finding is significant (p=0.0001).

McNemar Test for alcohol Consumption – N, P and Y individually

		Controls			
		N	P	Y	Grand total
Cases	N	8	0	4	12
	P	12	1	4	17
	Y	21	7	10	38
Grand total		41	8	18	67

McNEMAR TEST FOR TOBACCO AND ALCOHOL CONSUMPTION

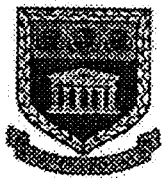
People who smoke usually drink and vice versa. The McNemar test (table 4.12 and table 4.13) and the Logistic regression analyses (table 4.14) are done to test the association.

McNemar Test for combined Alcohol or Tobacco consumption given equal weights

		Controls			
		N	P	Y	Grand total
Cases	N	11	3	1	15
	P	8	8	3	19
	Y	12	14	7	33
Grand total		31	25	11	67

Taking the frequencies above and below the diagonal it is clear that in 34 pairs the cases used alcohol and tobacco more than the controls and in 7 pairs above the diagonal the controls used alcohol and tobacco more than the cases. The finding is significant (P=0.001).

Appendix 5: ETHICAL CLEARANCE CERTIFICATE



Faculty of Dentistry & WHO Collaborating Centre for Oral Health

UNIVERSITY OF THE WESTERN CAPE

FACULTY RESEARCH COMMITTEE

ETHICAL CLEARANCE CERTIFICATE

REGISTRATION NO	02/6/6
PROJECT	**Risk of oral cancer associated with tobacco smoking and alcohol consumption: A case control study in the Western Cape, South Africa.**
PRINCIPAL INVESTIGATOR **SUPERVISOR** **CO-SUPERVISORS**	Dr Rajesh Chandran Dr NG Myburgh Dr Clare Stannard Prof Jos Hille
DEPARTMENT	Department of Community Oral Health Faculty of Dentistry University of the Western Cape
DATE CONSIDERED	23 May 2002
DECISION OF COMMITTEE	Approved unconditionally
DATE	23 May 2002

SIGNATURE

Prof MH Mobit
(Director: Dean)

Dr LXG Stephen
(Research & Publications Committee)

TEL: +27 21 370 4400 or +27 21 370 4418 FAX: +27 21 392 3250 EMAIL: lstephen@uwc.ac.za

ETHICS STATEMENT PROJECT (REF: 02/6/6)

The patient's / guardian's consent would be obtained and the patient / guardian would be informed of the nature of study. The patient / guardian would have the right to withdraw from the study. Any oral lesions detected during clinical examination, will be treated / referred for treatment. All information will remain strictly confidential.

To be completed in duplicate and ONE COPY returned to the Deans Office, 5th Floor, Oral Health Centre, Mitchells Plain.

I/we fully understand the condition under which I am / we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee.

DATE: 4 Sept 2002 **SIGNATURE:** .....

PLEASE QUOTE THE PROJECT REGISTRATION NUMBER IN ALL CORRESPONDENCE

TEL: +27-21-370 4490 or +27-21- 370 4413 FAX: +27-21-392 3760 EMAIL: lstiplan@uwc.ac.za

Appendix 6: PERMISSION TO CONDUCT THE RESEARCH

Department of Community Oral Health
Faculty of Dentistry & WHO Oral Health Collaborating Centre
UNIVERSITY OF THE WESTERN CAPE
Private Bag X09, Modderdam Plein 7785
CAPE TOWN

Tel: +27 21 979 4800
Fax: +27 21 392 3250

2 September 2002

Dr P J Mitchell
Chief Medical Superintendent
Groote Schuur Hospital
Observatory
7925

Dear Sir,

Dr Rakesh Chandran is currently registered as a Master of Science student with the University of the Western Cape. He is required to do a mini thesis as a requirement for the fulfillment of the course in Dental Public Health. As part of the data collection study he would like to interview patients who attend the Combined Head and Neck Clinic.

He has consulted with Prof T J Bills and Dr Chris Simmons who are his co supervisors for the project, obtaining their approval and support. They have also assisted him with making the necessary arrangements to assist the data collection process.

He would like to interview the patients between August and December 2002.

Kindly grant him permission to do the same.

Thanking you,

Dr Neil Myburgh
Postgraduate Research Supervisor
Director, WHO Collaborating Centre for Oral Health
Chair, Department of Community Oral Health

Research Ethics Committee
Faculty of Health Science
E46-26 Old Main Building, Groote
Schuur Hospital, Observatory, 7925
Queries : Xolile Fula
Tel : (021) 406-6492 Fax: 406-6411
E-mail : Xfula@curie.uct.ac.za

11 September 2002

REC REF: 291/2002

Dr C Stannard
Radiation Oncology

Dear Dr Stannard

RISK OF ORAL CANCER ASSOCIATED WITH TOBACCO SMOKING AND ALCOHOL CONSUMPTION: A CASE CONTROL STUDY IN THE WESTERN CAPE, SOUTH AFRICA

Thank you very much for submitting your study to the Research Ethics Committee for review.

*It is a pleasure to inform you that the Committee has formally **approved** your study, provided that you make minor amendments to the consent form as shown in the attachment.*

Please quote the above Rec. reference number in all correspondence

Yours sincerely

DR A ROBINS
DEPUTY CHAIRPERSON

ENQUIRIES / NAVRAE : Dr P.J. Mitchell
TELEPHONE / TELEFOON : (021) 404-6288
FAX / FAKS : (021) 404-3260
EMAIL : pmitchell@pawc.wcape.gov.za
REFERENCE / VERWYSING : 12RAT/Research
DATE / DATUM : 10 September 2002

PROVINCIAL ADMINISTRATION : WESTERN CAPE
Department of Health

PROVINSIALE ADMINISTRASIE : WES-KAAP
Departement van Gesondheid

ULAWULO LWEPHONDO : INTSHONA KOLONI
Isebe Lezempilo

Mr R. Chandran
P O Box 2065
BLOEMFONTEIN
9300

Dear Mr Chandran

RE : THESIS : ORAL CANCER

Many thanks for your letter of 5 September 2002.

I have referred it to Dr B. Jacobs : Medical Superintendent : Radiation Oncology for her attention and response to you.

Yours sincerely

DR P.J. MITCHELL
CHIEF MEDICAL SUPERINTENDENT

c.c. Dr B. Jacobs

/vms
c:\rad meds\oral thesis\chandran.c

Groote Schuur Hospital
Private Bag,
Observatory, 7925
Telephone: 404-9111

Groote Schuur Hospitaal
Privaatsak,
Observatory, 7925
Telefoon: 404-9111

NAVRAE	Dr. T. Numanoglu
TELEFOON	(021) 404-3169
FAKS	(021) 404-5291
VERW.	
REFERENCE	
DATUM	07 November 2002

PROVINCIAL ADMINISTRATION : WESTERN CAPE
Department of Health

PROVINSIALE ADMINISTRASIE : WES-KAAP
Departement van Gesondheid

ULAWULO LWEPHONDO : INTSHONA KOLONI
Isebe Lezempilo

To whom it may concern

Mr. Rakesh Chandran has received permission to interview patients in the Outpatient Department for the purpose of the research on the risk factors of oral cancer during the period of November 2002 to January 2003.

Yours sincerely,

DR. TUNÇ NUMANOGLU
MEDICAL SUPERINTENDENT
OUTPATIENT DEPARTMENT

TN/rc

Ref : OTN/Letters/General/R. Chandran

Groote Schuur Hospital
Private Bag,
Observatory, 7935
Telephone: 404-9111

Groote Schuur Hospital
Privaatsak,
Observatory, 7935
Telefoon: 404-9111