CIGARETTE SMOKING AND ALCOHOL INGESTION AS RISK FACTORS FOR OROPHARYNGEAL SQUAMOUS CELL CARCINOMA AT THE KENYATTA NATIONAL HOSPITAL.

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A dissertation submitted as partial fulfillment of the requirements by the University of Nairobi for the award of the degree of Master of Medicine in Otorhinolaryngology, Head and Neck Surgery.

DECLARATION

This is my original work. It has not been presented for a degree award at any other university.

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DEDICATION

This dissertation is dedicated to my loving family Mr. and Mrs. Mwangi, Kevin Linus, Dr. Mwangi and Susan Mwangi for their constant support, encouragement and prayers throughout the study.

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Thanks to the Almighty God for giving me the strength to finish this study.

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ACCRONYMS / ABBREVIATIONS

ADH:	Alcohol dehydrogenase
ALDH:	Aldehyde dehydrogenase
AJCC:	American Joint Committee on Cancer
CYPE2E1:	Cytochrome P450 2E1
DNA:	Deoxyribonucleic acid
ENT:	Ear Nose and Throat
ERC:	Ethics Research Committee
HDI:	Human development index
HPV:	Human papilloma virus
KDHS:	Kenya demographic and health survey
KNH:	Kenyatta National Hospital
NIAAA:	National Institute on Alcohol Abuse and Alcoholism
OPSCC:	Oropharyngeal Squamous cell Carcinoma
OR:	Odds ratio
SCC:	Squamous cell carcinoma
TGF:	Tumor growth factor
UON:	University of Nairobi
WHO:	World Health Organization

ABSTRACT

Background

Cancer is the third most common cause of deaths in adults in Kenya. According to the Nairobi cancer registry, cancer cases are steadily increasing. Oropharyngeal cancer accounts for 10-12% of head and neck malignancies. Squamous cell carcinoma (SCC) forms 90 per cent of oropharyngeal malignancies. Tobacco smoking and alcohol intake have a strong interactive effect on the risk of squamous cell carcinoma of the head and neck. Data availability on cancer epidemiology and etiology in Kenya is scanty and is mainly hospital based, therefore true burden is unclear.

Objective: To determine the role of smoking tobacco and alcohol consumption as risk factors in causation of oropharyngeal squamous cell carcinoma (OPSCC) at Kenyatta National Hospital (KNH).

Study Setting and Procedure

This was a hospital based case control study that was conducted in Kenyatta National Hospital E.N.T wards and clinics and radio-oncology unit and orthopedic unit. Data for a total of 65 patients with confirmed OPSCC was selected from a cohort of an ongoing prospective study while 130 controls matched for age and sex were recruited from the orthopedic unit. History of cigarette smoking and alcohol consumption was obtained and analyzed. In addition, the tumor characteristics among cases were also documented.

Results

Majority of the participants with OPSCC had multiple sub-sites involved (53.9%), with the tonsils being the most affected sub-site (60%). Tobacco smoking showed a significant association with OPSCC ($P < 0.001$) and odds of OPSCC was 3.6 times higher among smokers compared to participants who had never smoked. Stratification of smokers by current smoking status showed that compared to participants who had never smoked, current smokers were at highest risk of OPSCC (OR = 5.0; 95% CI 2.29-10.93) followed by those who had stopped smoking (OR = 2.85; 1.33-6.09). Alcohol consumptions did not have a significant association

with OPSCC (0.87); however there was an exponential increase in risk with increased intake. No synergism was demonstrated when joint exposure was assessed.

Conclusions and Recommendation

Cigarette smoking and alcohol consumption are risk factors for oropharyngeal SCC in patients seen at the Kenyatta National Hospital. Interventions targeted at reducing exposures need to be emphasized since a reduction in risk was noted with cessation and lower consumption of the same.

CHAPTER ONE

INTRODUCTION

1.0 Introduction

Cancer is a leading cause of death in both developed and developing countries; the burden is expected to grow due to growth and aging of the population as well as changing lifestyles. Based on Globocan statistics estimate, 14.1 million new cases and 8.2 million deaths occurred in 2012 worldwide [(1)]. Cancer burden in less developed countries account for about 57% of cases and 65% of cancer deaths worldwide.[(1)]

In Kenya, cancer ranks 3rd among the causes of death after infections and cardiovascular or heart related diseases. It accounts for up to 18000 deaths annually in Kenya. Incidence of cancer in Kenya is on the rise with over 82000 new cases reported annually.[(2)] A report by GLOBOCAN projects that Kenya could be having a prevalence of 82500 cancer cases and approximately 22000-25000 new cases per year [(1)].

Oropharyngeal cancer comprises 10-12% of head and neck cancers [(3)]. It is relatively uncommon, however it is a debilitating neoplasm that interferes with feeding, speech and also the airway is at risk. Squamous cell carcinoma (SCC) accounts for 90% of all histological types of oropharyngeal carcinoma [(3)].

Over the past three decades, there has been a change of trend where the younger adults are increasing being more affected and there is equal gender distribution. This has been attributed to the role of human papilloma virus (HPV) in tumorigenesis in oropharyngeal carcinoma [(4)].

1.1 Background

1.1.1 Applied Anatomy

The oropharynx lies at the level of the 2nd and 3rd cervical vertebrae and is part of the myofascial pharynx. Along with being continuous with oral cavity anteriorly, it is continuous with nasopharynx superiorly and hypopharynx inferiorly[(5)].

The boundaries of the oropharynx are superiorly the junction of hard and soft palate, inferiorly the level of the plane of the hyoid bone and anteriorly the junction of anterior 2/3 and posterior 1/3 tongue at the level of circumvallate papillae.

It is lined with stratified squamous cell epithelium which is non keratinized. The oropharyngeal epithelium is part of the aerodigestive tract and is constantly bombarded by both airborne and ingested carcinogens. Due to chronic irritation, there may be areas of parakeratin and orthokeratin. These areas may result to progressive dysplasia leading to carcinoma in situ and ultimately invasive carcinoma. Precancerous lesions that result include erythroplakia, leukoplakia and lichen planus.

ONCOLOGIC SUBSITES

The oropharynx is divided into five oncologic sub sites that include:

1. Soft palate and uvula
2. Palatine tonsils and tonsillar fossa
3. Base of tongue
4. Vallecula
5. Lateral and posterior oropharyngeal walls

The myofascial layers are made up of 3 paired constrictors (superior, middle and inferior) and covered internally by the pharyngobasilar fascia and externally by the buccopharyngeal fascia. Laterally is the parapharyngeal space which is divided into prestyloid and poststyloid compartment by a stylopharyngeal fascia. The parapharyngeal space contains carotid sheath and its contents, cranial nerves IX through XII and the sympathetic chain and thus extension of tumor laterally may result to neurologic deficits and encasement of the blood vessels. Neural infiltration and encasement of blood vessels are an issue of diagnostic and functional importance.

Posteriorly, the pharyngobasilar fascia acts like a natural barrier to tumor extension to prevertebral fascia and thus provides a clear plane of resection. However, if tumor breaches this fascia, it extends to prevertebral tissue and is unresectable.

Motor innervation is by pharyngeal plexus that is composed of pharyngeal branches of glossopharyngeal and vagus nerve [(5)].

Most distinguishing characteristic is that it is the location for most of waldeyer's lymphatic ring including lingual and palatine tonsils [(6)]. Its significance in oropharyngeal tumorigenesis is that it entraps mainly lymphotrophic viruses which also cause metaplastic change and squamous cell tumorigenesis OPSCC has high propensity for nodal metastases and 50% of patients have clinically palpable nodes, while 25% have an occult metastases at the time of presentation [(6)].

Oropharyngeal cancer incidence has increased because of HPV induced tumors. However, smoking and alcohol still remain the two major risk factors implicated in oropharyngeal carcinoma.

SCC is the most common malignancy and forms 90 per cent of the tumors in this region. Non-Hodgkin's lymphomas account for 8 per cent and minor salivary gland tumors for 2%[(7)]. In addition to the differentiated keratinizing and nonkeratinizing SCC, specific histopathology variants are found: verrucous, basaloid squamous cell, spindle cell, adenosquamous, and undifferentiated carcinomas[(7)].

With regard to oropharyngeal squamous cell carcinoma, the frequency of sites affected is as illustrated below.

Table 1: Frequency of cancer involvement in the different oropharyngeal subsites

SITE	FREQUENCY (%)
Tonsil/ lateral wall	60
Base of tongue	25
Soft palate	10
Posterior wall	5

Courtesy of Stell and Maran's Textbook of Head and Neck Surgery and Oncology[(6)]

The most common system utilized in classification of oropharyngeal squamous cell carcinoma is with the staging guidelines of American Joint Committee on Cancer (AJCC) [8].

1.2 Pathophysiology

Major carcinogens clinically associated with the development of squamous cell carcinoma of mucosa of the upper aerodigestive tract include tobacco products and alcoholic beverages. The relative contribution of these two major carcinogen groups depend on: - [9]

1. Type of carcinogen
2. History of exposure
3. Anatomic site in which the neoplastic transformation occurs

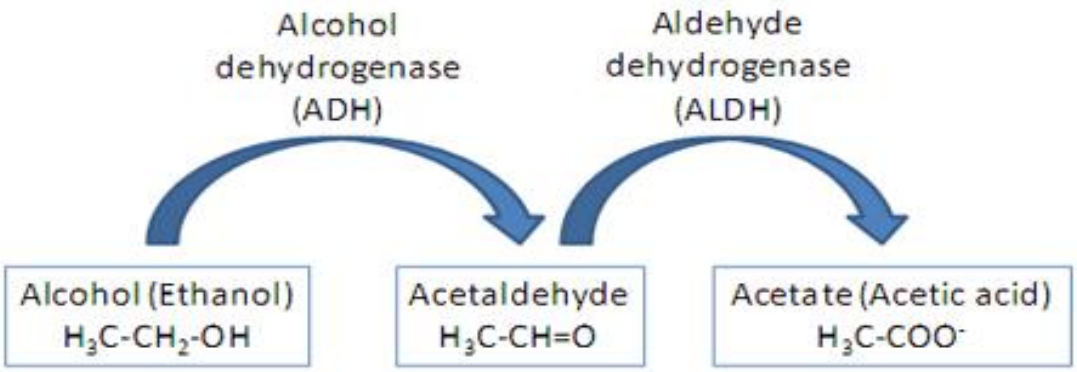
Relative risk for oropharyngeal carcinoma increases with amount of alcohol and tobacco consumed. Studies have demonstrated that they have a synergistic effect because when both are used together, there is a much higher incidence of neoplasia than when either is used alone [7].

Long exposure to these carcinogens results in extremely damaged mucosa with numerous types of genetic alterations referred to as field effect or field cancerization where extensive dysplastic changes occur in a wide epithelial region. Genetic predisposition may influence the cancer risk of alcohol. This is related to alcohol metabolism which is genetically predetermined and is a result of different enzymatic alleles [10].

Three enzyme groups are involved in alcohol metabolism namely:

1. Alcohol dehydrogenase (ADH)
2. Aldehyde dehydrogenase (ALDH)
3. Cytochrome P450 2E1 (CYP2E1)

Figure 1: Alcohol metabolism[11]



Different alleles of these enzymes exist and usually having varying enzymatic activity. Acetaldehyde is a carcinogen in humans and thus increasing levels of it, e.g. in people with alleles ADH1C and ALDH2 which have high and very low enzymatic activity respectively, result in increased cancer risk [(10)].

The normal oral bacterial flora is altered by both alcohol and smoking resulting in bacterial species that can metabolize ethanol to acetaldehyde. Acetaldehyde results in excessive growth of mucosal cells in the upper digestive tract [(11)]. Chronic alcohol consumption result in epithelial atrophy and hyper regeneration of the oropharyngeal mucosa associated with hyperchromatic cell nuclei of the basal cell layer. It promotes carcinogenesis by interfering with DNA replication as result of alterations ranging from point mutations to gross chromosomal alterations [(12)].

It also impairs reparative process of damaged DNA. Moreover, it can interact with the bases resulting in DNA adducts which may trigger replication errors, interfere with tumor suppressor genes and form oncogenes. Acetaldehyde is found in saliva and the oropharyngeal cancer risk is dose dependent. Patients with oropharyngeal cancer have been noted to have elevated acetaldehyde concentration in their saliva [(13)].

Saliva has been implicated to having a pivotal role in pathogenesis of oropharyngeal carcinoma according to Reznick et al. Saliva has redox active metals that react synergistically with low

reactive free radicals in cigarette smoke, which results in the production of highly active hydroxyl free radicals [14].

An accepted concept of oropharyngeal carcinoma induced by cigarette smoke is based on cellular and DNA aberrations eventually leading to malignant transformation and cancer development due to a constant irritation of various cigarette smoke carcinogens [14].

Over 300 tobacco carcinogens have been evaluated and include polycyclic aromatic hydrocarbons, nicotine derived nitrosamines, aromatic amines, heterocyclic amines and many more. Two important classes implicated in oral and oropharyngeal cancers include the polycyclic hydrocarbons and nicotine derived nitrosamines which usually cause p53 mutations. P53 is a tumor suppressor gene which on mutations loses its efficacy and paralysis of apoptotic process occurs resulting in unchecked abnormal cellular growth resulting to malignant cells.

Alcohol has also been implicated as a solvent for carcinogenic chemicals in smoke products [15].Smoking on the other hand, also does increase acetaldehyde by:-

1. Increasing the capacity of oral yeast and bacteria to produce acetaldehyde from ethanol.
2. Cigarette smoke itself contains considerable amounts of aldehyde that dissolves in saliva [16].

In addition, tobacco contains nitrosamines which cause DNA damage in epithelial cells in the oropharynx by deregulating the cell cycle. This is as a result of molecular changes which include p53 gene mutation, activation of telomerase, formation of defective DNA adduct and expression abnormalities of TGF beta signaling pathway. They produce DNA adducts principally 6 methyl guanine, which interfere with DNA replication [17]. Alcohol causes induction of liver enzymes including CYP2E1 which metabolizes tobacco pro carcinogens to their carcinogenic metabolites that further augments carcinogenesis.([11]

From the carcinogenic effect of tobacco and alcohol, the oropharyngeal mucosa forms preneoplastic lesions which are considered to have a sequential continuum towards disease. In precursor lesions, the cessation of smoking doesn't remove the potential for progression of the disease and patients must be followed indefinitely. However, smoking cessation reduces the relative risk of oropharyngeal cancer [17].

The incidence of oropharyngeal carcinoma has been on the rise due human papilloma type 16 associated oropharyngeal cancers. It has been referred to as an epidemic of HPV oropharyngeal cancer. The young age group has been the most affected as the epidemic has implicated sexual behaviors as one of the incriminated causes. The normal habitat of HPV is the anogenital region and thus practices such as oral sex and oroanal sex have the capacity to infect the oral cavity with HPV virus through transfer. Studies on the impact of HPV are being done with one currently ongoing in the E.N.T department KNH on the impact of HPV on head and neck cancers.

Other risk factors implicated in oropharyngeal carcinoma are previous irradiation, poor oral hygiene, diet low in fruits and vegetables and a vitamin A deficiency. Nutritional plays a major role in cancer development. A diet low in fruits and vitamin A deficiency has been associated with cancer. Vitamin A inhibits DNA in malignant cells and thus inhibits malignant cells proliferation.

1.3 Literature Review

Literature on OPSCC in Kenya is scarce. Nairobi cancer registry is unreliable as it condenses hospital based literature which may not be representing the population as Kenyatta National Hospital is the national referral hospital. In Kenya, there is the Cancer Prevention and Control Act Cap 246B that outlines how medical institutes having made a diagnosis of cancer should notify the national cancer registry institute and thus provide a more population based registry than hospital based.[18] Unfortunately this act has not been executed and no effective Cancer Institute exists and the true incidence and prevalence of cancer in Kenya is not clear. Globally, several studies have been done. Oropharyngeal carcinoma in itself is not a common cancer as regards head and neck cancers and thus most research studies are done on oral cancer which combines the oral cavity and oropharyngeal region.

According to Mwansasu C et al in a study done in Tanzania, oropharyngeal carcinoma accounted for 9.7 % of the head and neck cancers and 91% were squamous cell carcinoma [19].

In Kenya, Onyango et al did a retrospective study on oral cancer which also constituted the oropharynx and noted that with regards to oropharyngeal region, prevalence was more in males as compared to females at a ratio of 2:1 respectively [20]. In South Africa, Ndui MK et al analysed epidemiology of oral cancer in South Africa and noted male to female ratio as being 3:1[21]. Limitation of the above studies is that true epidemiology of OPSCC is not revealed as the studies also included the oral cavity proper.

Numerous studies have demonstrated that alcohol and tobacco consumption increase the risk of oral cancer in a dose related fashion.

Rajesh P. et al conducted a population based case control study in India in which he studied different tobacco habits and the resultant risk of lung, oropharyngeal and oral cavity cancer development. Among the cases, 247 confirmed oro-pharyngeal cancer cases were extracted from the Bhopal cancer registry. Data on tobacco habits such as chewing or smoking were noted. Odds ratio (OR) =7.1 for oro-pharyngeal cancer in patients who had smoked tobacco. A marginal increase was noted with combination of tobacco smoking and chewing to OR= 7.3. The risk of development of OPC was dose dependent in relation to tobacco. The odd ratio implicated in tobacco consumption is not surprisingly high due to other different tobacco consumption habits such betel chewing in India that renders oropharyngeal and oral cavity tumor prevalence to be high in comparison to the rest of the world[(22)].

A case control study conducted by William J. et al conducted in the United States studied the relation of tobacco and alcohol use to oral and pharyngeal cancer. 1114 cases and 1268 controls were chosen and via a designed structured questionnaire, tobacco and alcohol consumption habits collected. These included type of alcoholic drink and amount consumed as well as the amount of tobacco smoked. The OR for OPC was calculated. In heavy drinkers >30drinks/wk, OR for OPC=8.8 while the OR in smoking for patients who had smoked 20-39 cigarettes per day was 2.1. These authors were able to demonstrate the multiplicative synergism between smoking and alcohol consumption on OPC, in that among those that smoked two or more packs of cigarettes and four or more drinks per day; there was an observed 35-fold increase in the risk of OPC. The authors estimated that smoking and drinking combined account for about 75% of all OPC in the United States [(23)]. Similar findings were noted by Franceschi et al where they demonstrated the comparative effect of alcohol and smoking exposure to the oral cavity and pharynx also demonstrated the synergism between the two risk factors. The found out that for the highest level of drinking (>77 drinks/week) and smoking (>25cigarettes/day), the OR for oral cancer was 3.4 and for pharyngeal cancer was 3.6. Interestingly, the risk for oral cancer was noted to be greater than in pharyngeal cancer when alcohol consumption increased while smoking level was stable. In this study, the odds ratio for oral cancer was about 2 times greater than for pharyngeal cancer for each combined level of drinking and smoking [(24)].

In Italy and Switzerland, Rodriguez T. et al analyzed data from two case control studies that included 137 cases and 298 controls. Risk factors analyzed for oral and pharyngeal cancers in young adults included smoking tobacco, alcohol consumption and diet. The multivariate odds ratios (OR) were 20.7 for heavy smokers and 4.9 for heavy drinkers. The combination of high tobacco and alcohol consumption led to an OR of over 48. Of all cancer cases in this population, tobacco accounted for 77%, alcohol for 52%, and low vegetable consumption for 52%, and the combination of the three factors for 85%[25].

The effects of tobacco smoking and alcohol drinking on cancer of the oral cavity and oropharynx were also evaluated among US veterans. The odds ratio was directly proportional to the increasing levels of tobacco and alcohol consumption. The synergistic effect was also demonstrated as in other studies. Interestingly, there was a plateau at the dose response curve at very high levels of tobacco or alcohol exposure. It was postulated that this may be as result of saturation of the mechanisms implicated in tobacco or alcohol related carcinogenic process on the oral mucosa. The odd ratios in this study are not also comparable with other studies as the reference group was heavy drinkers and smokers. Variations might also arise due to different composition of the alcohol and tobacco products [26].

Altieri et al. also reported that alcohol use as a risk factor associated with oral and pharyngeal cancers. Consumption of all types of alcoholic beverages increased a person's risk for oral and pharyngeal cancer. Those who consumed 3-4 drinks a day were at a 2.1 times higher risk for oral and pharyngeal cancer, 5-7 drinks 5 times higher, 8-11 drinks 12.2 times higher, and 12 or more drinks a day 21.1 times higher risk. There was a significant trend across the levels of drinking ($p<0.0001$) among those who consumed beer or spirits, and no wine. Wine had the most significant single effect on oral pharyngeal cancer risk, with those with higher alcohol consumption having higher risk [27].

Hashibe et al. concluded that in industrialized areas, it has been well-established that tobacco use and alcohol consumption account for roughly 75% of all cases of oral and pharyngeal cancers. Tobacco and alcohol use commonly occur together, which makes it is difficult to attribute risk to either alcohol or tobacco alone. Among smokers who have never used alcohol, the risk of oral and pharyngeal cancer is 2.13 times higher than persons who have never used alcohol or smoked [28]. In addition, alcohol consumption has been shown to be associated with increased odds of OPC among never smokers. Fioretti et al examined 42 cases of OPC among never smokers and

found that the major risk factor for OPC in never smokers was alcohol consumption, with an OR three-fold higher in drinkers than non-drinkers. A direct relation was also found for the duration of the habit, with an OR of 3.6 (95% confidence intervals, CI, 1.2-11.2) for drinking for 35 years or longer [29]. These are important studies in literature because they establish the independence that smoking and drinking have on the development of OPSCC.

CHAPTER TWO

STUDY JUSTIFICATION

2.0 Study Justification

Oral and pharyngeal cancer, grouped together, is the sixth most common cancer in the world [30].

Alcohol abuse and tobacco use are closely related to incidence of oropharyngeal squamous cell carcinoma. As countries with low and medium level human development index advance through societal and economic changes, they are likely to adopt different cultural practices. As such, the pattern of cancer incidence is likely to follow that seen in developed countries [31].

Kenya itself has had a rise in the human development index (HDI) by 0.004 from 2014 to 2015. As per December, 2015 HDI was 0.548. Cigarette smoking and alcohol consumption has been increasing steadily in Kenya (KDHS 2003). Shisha is one of the most commonly used emerging drug that has a high prevalence of abuse and 1 puff has been equated to 100 puffs of cigarette smoke [32].

Alcohol intake and cigarette smoking are documented risk factors for head and neck cancers. Data on head and neck cancer is scarce in the developing countries. Most data are from hospital based registries or case series as opposed to the gold standard of population based series [33]. In 2006 by Onyango et al in a retrospective descriptive study of patterns of head and neck cancers in KNH found a 55% intake of alcohol consumption and smoking among the patients [34] There is limited data the impact of drinking alcohol and tobacco smoking as risk factors in addition to other possible risk factors to oropharyngeal carcinoma in our setting.

2.1 Research Question

What is the role of smoking tobacco and alcohol consumption in causation of oropharyngeal squamous cell carcinoma at KNH?

2.2 Objectives

2.2.1 Broad Objective

To determine the role of smoking tobacco and alcohol consumption in causation of oropharyngeal squamous cell carcinoma at Kenyatta National Hospital (KNH).

2.2.3 Specific Objectives

1. To determine the odds attributed to tobacco smoking as a risk factor to development of oropharyngeal squamous cell carcinoma.
2. To determine the odds attributed to alcohol ingestion as a risk factor to development of oropharyngeal squamous cell carcinoma.
3. To determine demographic characteristics of patients with oropharyngeal squamous cell carcinoma.
4. To determine the prevalence of smoking tobacco and alcohol ingestion among patients with oropharyngeal squamous cell carcinoma.

CHAPTER THREE
METHODOLOGY

3.1 Study design

A hospital based matched case control study was conducted covering a 5 year period. This design was chosen as it is ideal for studying rare outcomes and thus was selected because of the rarity of oropharyngeal cancer in Kenyatta National hospital.

3.2 Study setting

The cases data were extracted from an ongoing prospective study [35] that is being conducted within the E.N.T department and radio-oncology unit, within KNH which has the bulk of patients with oropharyngeal cancer as they are the diagnostic and initial management points for most oropharyngeal cancer patients seen at the hospital. Controls on the other hand, were recruited from the orthopedic unit at KNH.

3.3 Sample size

The case: controls = 1:2

The cases and controls were matched according to age and sex.

Desired sample size was calculated using the **Kirkwood Formula for difference in proportions** [36]:

$$n = \left(\frac{r+1}{r}\right)\frac{(\bar{p})(1-\bar{p})(Z_{\beta}+Z_{\alpha/2})^2}{(p_1-p_2)^2}$$

Sample size assumptions;

- *The case: control = 1:2*
- *For 80% power, $Z_{\beta}=0.84$*
- *For 0.05 significance level, $Z_{\alpha/2}=1.96$*
- *r =2(ratio of control to cases)*

- $p_1 =$ *The proportion of controls who smoke tobacco* **78%**
- $p_2 =$ *Proportion of cases with oropharyngeal cancer and smoking* **98%**
- $\bar{p}$ *= average proportion* **(93+78)/2=85.5%**

Proportions are derived from a study done by William J. Blot, Joseph K. mc Laughlin et al on Smoking and drinking in relation to oral and pharyngeal cancer.

Therefore,

$$n = \left(\frac{2+1}{2}\right)\frac{(0.855)(1-\overline{0.855})(0.84+1.96)^2}{(0.78-0.93)^2}$$

Sample size of case obtained= 65 cases

Sample size of controls = 65*2 = 130 controls

3.4 Study population

Cases

Recruitment of the cases was done through selecting OPSCC patients from an ongoing prospective study on Solid Tumor Research Project- Head and Neck Registry; that is extracting data from customized head and neck oncology health records within the E.N.T and radiotherapy unit ([35]).

Controls

The recruitment of the controls was done from the orthopedic unit. The controls constituted subjects without oropharyngeal cancer and were matched to cases for age and sex which are established strong determinants of OPSCC.

3.5 Study procedure

3.5.1 Recruitment of cases

A total of 65 cases whose histopathology had been confirmed to be squamous cell carcinoma, oropharyngeal carcinoma were recruited for the study. The recruitment was done during an ongoing prospective study that is developing a Solid tumor head and neck registry in which data has been collected over a period of time.

The oropharyngeal squamous cell carcinoma was confirmed with histopathology results. The tumor staging had been staged clinically and radiologically by computerized tomography scanning or magnetic resonance imaging according to the AJCC staging system.

The participants had to have undergone an assessment for metastases using a chest radiograph, computerized tomography and or abdominal ultrasound as and when deemed necessary.

3.5.2 Recruitment of controls

The ratio of control to cases was 1:2 and thus a total of 130 controls were recruited. Recruitment of the cases was from the orthopaedic unit which includes the clinic and wards, and included patients with varying fractures and orthopaedic conditions. The subjects were selected through consecutive sampling at a point of time. After obtaining an informed consent, the recruits underwent an ENT examination to rule out any oropharyngeal lesions. None of the recruited controls were noted to have any oropharyngeal lesion. Controls were matched by sex and age with the cases within a range of three years.

3.5.3 Inclusion Criteria.

1. All cases with histological confirmed OPSCC.
2. All controls who give consent to participate in the study.

3.5.4 Exclusion Criteria

1. Cases with other histological diagnosis other than OPSCC.
2. Cases without any histological diagnosis.
3. Controls who decline to give consent to participate in the study.
4. Controls noted to have suspect oropharyngeal lesions.
5. Cases with incomplete data.

3.5.5 Data collection and standardization

Cases:

Data for the cases included demographic characteristics, alcohol consumption, tobacco smoking history and tumour characteristics.

Alcohol intake habits, including the type, duration and amount, were categorized as per NIAAA guidelines as to whether they are non drinkers, social, moderate or heavy drinker [(11)].

Cigarette smoking duration, type and amount were recorded and classified in pack-years.

The oropharyngeal sub sites affected with OPSCC were documented and differentiation characteristic also recorded. Due to the varying TNM stages noted, the cases were further stratified according to prognostic stages I-IV.

Controls:

An informed consent was sought from selected controls from the orthopaedic unit. A physical examination of the oropharynx was done by the principal investigator to rule out suspect oropharyngeal lesions and none was found with any suspect lesions, and thus none of the participants was referred to the ENT unit for further evaluation, diagnosis and management.

The principal investigator then proceeded to interview the controls and a pretested preformatted data collection questionnaire was filled. Demographic data including age, sex, and region of origin, tobacco smoking and alcohol intake were collected.

Similar to the cases, alcohol intake habits, including the type, duration and amount, were also categorized as per NIAAA guidelines as to whether they were non drinkers, social, moderate or heavy drinker [11]. Cigarette smoking duration, type and amount was also recorded and classified in pack-years.

3.5.6 Data management

All data retrieved were handled with utmost privacy. The data were de-identified so as to maintain confidentiality.

The principal researcher retrieved the data from the completed questionnaires and entered it into a password secured Microsoft Access database. Data from the questionnaire were crossed checked against the database for any inconsistencies and data entry errors and appropriate corrections were made.

3.5.7 Data analysis

The data thereafter was exported to SPSS 18.0 statistical package which was used for subsequent data analysis.

The analysis plan was based on the study objectives and comprised three broad types of analysis: univariable analysis, bivariate analysis and multivariable regression analysis. Mean, median and standard deviation were calculated for each continuous variable in the univariable analysis. These statistics were used to summarize continuous variables like age, duration of exposure to risk factors of oropharyngeal cancer e.g. smoking. Counts and proportions were used to summarize categorical variables in the univariable stage for example to describe the sex distribution of cases among other categorical demographic characteristics.

In the next stage involving bivariate analysis, Chi squared and Fisher's exact tests were performed to detect associations between categorical variables and oropharyngeal cancer diagnosis whereas ANOVA and T tests were used to detect associations between continuous variables and oropharyngeal cancer.

Multivariable logistic regression methods were used to detect independent predictors of oropharyngeal cancer. The factors included in the logistic regression were the primary exposures of tobacco smoking and alcohol ingestion and other risk factors that showed significant association with case-control status in the bivariable analysis. Statistical significance was based on a p value cutoff of 0.05.

Results were presented in tables, graphs, and pie charts. The findings of the study will be disseminated through scientific presentations at conferences, and departmental academic meetings, and also through publication in peer reviewed scientific journals.

3.5.8 Study limitations

Insufficient recording of relevant data was one of the study limitations encountered and all cases noted to have insufficient data were excluded from the study.

Selection bias was exempted by recruiting only histological confirmed oropharyngeal squamous cell carcinoma cases.

Examination and interviewing of the cases was over a period of time by different individuals prior to them being placed in the database that is being developed on solid tumors within the department. The controls' data on the other hand were collected at one point of time by the principal investigator. This may cause disparities in the data collected and one may not fully rule out differences in the populations' exposure at the different times.

Other biases such as recall bias may influence the data with regards to alcohol consumption and tobacco smoking as the recruits may give lower estimates of the exposures.

3.5.9 Quality Control

Quality control was implemented as a continuous process throughout the study to maximize validity and reliability of the findings of the study.

A pre-test of the structured questionnaire was carried out by clarifying grammar and language used so as to avoid bias and misinterpretation of the questions. The principal investigator solely carried out all the physical examinations of the controls and interviews. The data collection tools were cross checked for completeness and any missing entries corrected. The quantitative and qualitative data collected were cross checked for any inconsistencies and outliers rectified.

3.5.10 Ethical considerations

This study was reviewed and approved by the Kenyatta National Hospital and University of Nairobi Ethics & Research Committee. Approval reference no: P626/08/2016. The participants recruited as controls received full disclosure of the nature of study before any informed consent was taken. No persons with diminished autonomy such as individuals under 18years of age were found in this study. Patients who declined to participate were not discriminated and continued to receive treatment as those who were participating in the study.Informed consents were given before proceeding to fill the questionnaires. Potential participants were informed participation in the study was voluntary. On recruitment of appropriate respondents, de-identification was done before proceeding to fill the questionnaires.

Confidentiality was maintained throughout the research period. No extra cost was incurred by the participants. There are no conflicts of interest financial or otherwise in this study by the principal investigator, supervisors and the hospital. This study was self funded.

The results of the study shall be disseminated through scientific presentations at conferences, and departmental academic meetings, through publications in peer reviewed scientific journals and even regular newspapers where necessary.

At the end of the study, the raw data shall be destroyed and deleted from any existing hard copies by paper shredding and formatting and deleted from any soft copy storage devices including computers, flash discs and hard disks.

CHAPTER FOUR

RESULTS

4.1 Results

Demographic characteristics of patients with oropharyngeal squamous cell carcinoma

The sample comprised a total of 195 patient including 65 cases and 130 controls. The male-to-female ratio of cases of oropharyngeal squamous cell carcinoma in KNH was 4: 1 with 52 males (80%) and 13 females (20%) recruited as cases and followed by a corresponding ratio of sex-matched controls (Table 1). The mean age of the cases was 58.6 (± 14.1) years compared to a mean age of 56.4 (± 13.4) years for controls. The modal age groups for cases of oropharyngeal cancer was 60-69 years (32.3%) and among controls the modal age groups were 50-59 years (28.5%) and 60-69 years (28.5%).

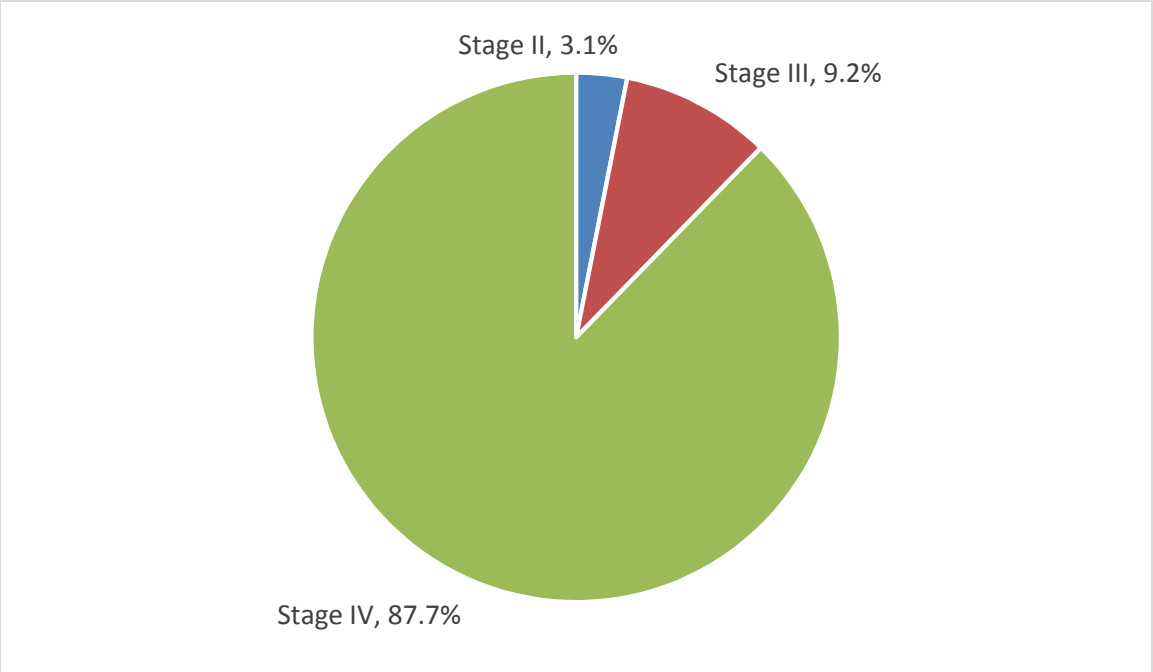
Table 2: demographic characteristics of patients with oropharyngeal squamous cell carcinoma and controls

	Cases	**Controls**	**OR (95% CI)**	**P**
Age				
< 40 years	7(10.8)	17(13.1)		
40-49 years	7(10.8)	21(16.2)	0.81(0.24-2.76)	0.736
50-59 years	17(26.2)	37(28.5)	1.12(0.39-3.19)	0.838
60-69 years	21(32.3)	37(28.5)	1.38(0.49-3.86)	0.542
70 years +	13(20.0)	18(13.8)	1.75(0.56-5.45)	0.331
Sex				
Male	52(80.0)	104(80.0)		
Female	13(20.0)	26(20.0)	1.00(0.48-2.11)	1.0

Presentation of oropharyngeal squamous cell carcinoma

Staging of oropharyngeal SCC among the cases (n = 65) is presented in figure 1. The majority (87.7%) of cases presented with stage IV SCC and the remaining cases had either stage III (9.2%) or stage II (3.1%) SCC.

Figure 2: Stages of oropharyngeal squamous cell carcinoma in cases identified in KNH



There were 30 (46.2%) well differentiated cancers among the 65 identified cases as shown in table 2. Undifferentiated cancers occurred in 10 (15.4%) cases while the remaining cases showed poor 9 (13.8%) or moderate 16 (24.6%) differentiation.

Table 3: Histology of oropharyngeal SCC in cases identified in KNH

	Frequency (n)	**Percent (%)**
Histologic findings of oropharyngeal SCC		
Undifferentiated	10	15.4
Poorly differentiated	9	13.8
Moderately differentiated	16	24.6
Well differentiated	30	46.2

There was no evidence of a significant association between oropharyngeal SCC staging and the findings of histology, P = 0.509 (table 3). Most oropharyngeal carcinomas within each level of differentiation were stage IV (between 80 and 100% for each level).

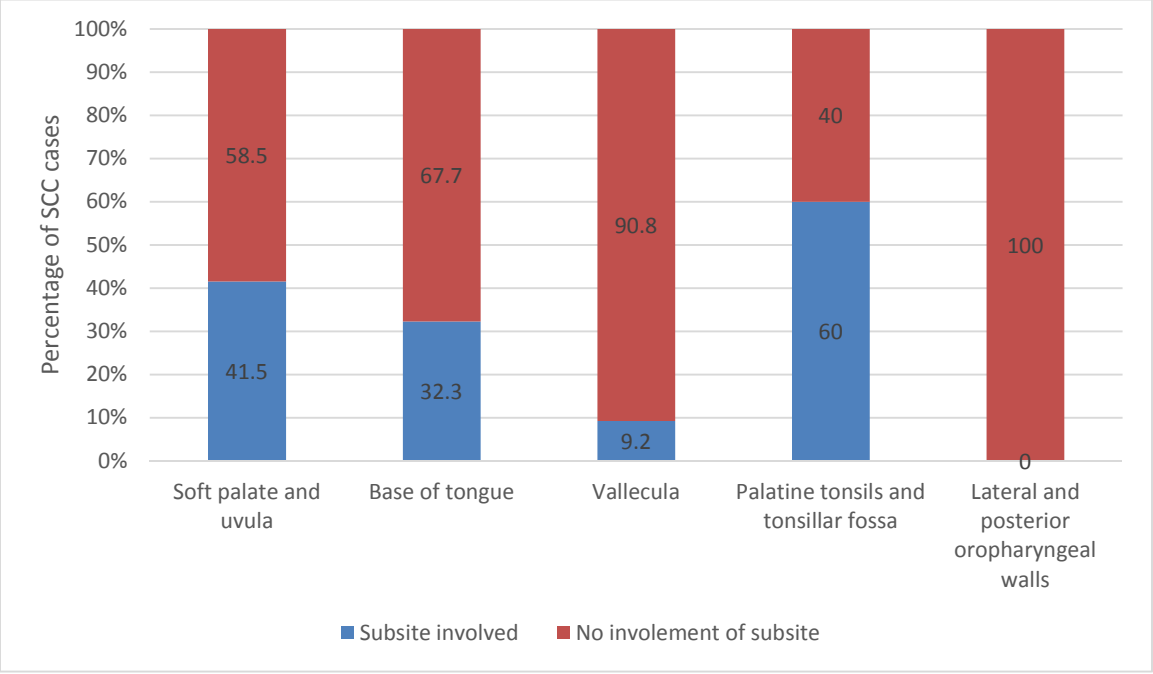
Table 4: Staging of oropharyngeal SCC and its association with histology findings

	Undifferentiated n (%)	Poorly differentiated n (%)	Moderately differentiated n (%)	Well differentiated n (%)	P
Stage					
II	1(10.0)	0(0.0)	0(0.0)	1(3.3)	0.509
III	1(10.0)	0(0.0)	3(18.8)	2(6.7)	
IV	8(80.0)	9(100.0)	13(81.3)	27(90.0)	

Subsite involvement

Among the 65 cases of oropharyngeal carcinoma there were 35 (53.9%) with cancers showing multiple subsite involvement. Of the oropharyngeal sites that were examined palatine tonsils and tonsillar fossa was the most commonly involved site in oropharyngeal SCC in 60% of the cases (Figure 2). There were no cancers that involved the lateral and posterior oropharyngeal walls.

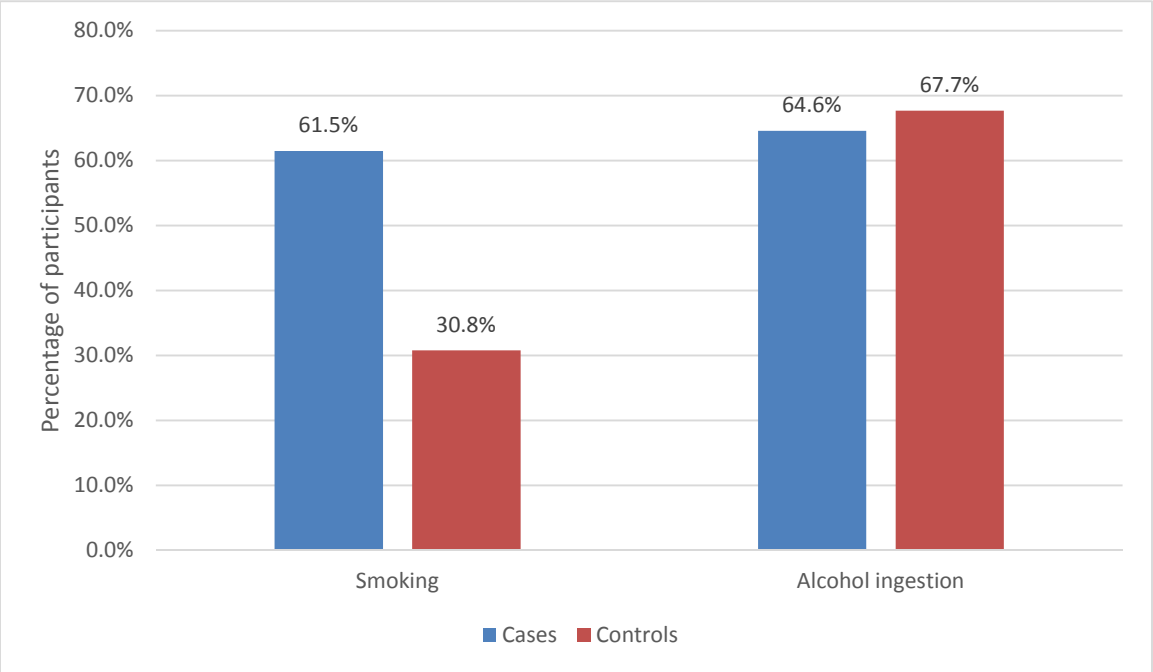
Figure 3: Subsite involved in oropharyngeal carcinoma among cases in KNH



Prevalence of smoking tobacco and alcohol ingestion among patients with oropharyngeal squamous cell carcinoma

Out of the 65 cases of oropharyngeal SCC 61.5% reported any history of lifetime smoking compared to 30.8% of the controls (Figure 2). The prevalence of alcohol consumption was 64.6% among the oropharyngeal carcinoma cases compared to 67.7% among the controls.

Figure 4: Prevalence of smoking tobacco and alcohol ingestion among patients with oropharyngeal squamous cell carcinoma and controls



The participants who reported that they were smokers had 28.3% higher risk of oropharyngeal SCC compared to those who reported not smoking (Attributable risk 28.3 per 100). The attributable risk percent was 56.5% representing a 56.5% increase in the risk of carcinoma due to smoking. This increase represents a population attributable risk of 34.8% implying a 34.8% reduction in the risk of oropharyngeal SCC in the population if smoking was eliminated.

Tobacco smoking as a risk factor to development of oropharyngeal squamous cell carcinoma

Tobacco smoking shows a significant association with oropharyngeal SCC ($p < 0.001$). As shown in table 4, the odds of carcinoma among cases reporting ever having smoked was 3.6 times higher than that of participants who had never smoked (OR 3.6, 95% CI 1.93-6.71).

Current smokers were at 5 times higher risk of SCC compared to nonsmokers (OR = 5.0, 95% CI 2.29 - 10.93, $p = 0.007$) while participants who had quit smoking had a two to three-fold increase in risk of SCC compared to nonsmokers (OR = 2.85, 95%% CI 1.33 – 6.09, $p < 0.001$).

Table 5: Tobacco smoking as a risk factor to development of oropharyngeal squamous cell carcinoma

	Cases	**Controls**	**OR (95% CI)**	**P**
Ever smoked				
No	25(38.5)	90(69.2)		
Yes	40(61.5)	40(30.8)	3.60(1.93-6.71)	<0.001
Current smoking status				
Never smoked	25(38.5)	91(70.0)		
Stopped smoking	18(27.7)	23(17.7)	2.85(1.33-6.09)	0.007
Current smoker	22(33.8)	16(12.3)	5.00(2.29-10.93)	<0.001

Alcohol ingestion as a risk factor to development of oropharyngeal squamous cell carcinoma.

Overall, there was no significant association between alcohol consumption and risk of oropharyngeal SCC (OR = 0.87, 95% CI 0.47 – 1.63, $p = 0.668$), table 5. However, based on the NIAAA classification participants who reported very heavy alcohol consumption were at significantly higher risk of oropharyngeal SCC (24.6% versus 4.6%). The odds of SCC were five times higher (OR = 5.22, 1.80 – 15.12) in very heavy drinkers compared to participants who did not consume alcohol.

Table 6: Alcohol ingestion as a risk factor to development of oropharyngeal squamous cell carcinoma

	Cases	Controls	OR (95% CI)	P
Alcohol ingestion				
No	23(35.4)	42(32.3)		
Yes	42(64.6)	88(67.7)	0.87(0.47-1.63)	0.668
Level of alcohol consumption (NIAAA classification)				
Nil	23(35.4)	45(34.6)		
Light	4(6.2)	35(26.9)	0.22(0.07-0.71)	0.011
Moderate	10(15.4)	31(23.8)	0.63(0.26-1.51)	0.301
Heavy	12(18.5)	13(10.0)	1.81(0.71-4.59)	0.214
Very heavy	16(24.6)	6(4.6)	5.22(1.80-15.12)	0.002

Alcohol and tobacco as joint exposures as risk factors for oropharyngeal squamous cell carcinoma

Majority of the participants of the study consumed both alcohol and smoked tobacco and had 1.95 times risk of OPSCC (OR = 1.95 95% CI 0.96 – 3.93, p = 0.063). Alcohol consumption alone was associated with a 0.20 risk while smoking alone has a higher risk association three times risk.

TABLE 7: Alcohol and tobacco as joint exposures as risk factors for oropharyngeal squamous cell carcinoma

	Cases	Controls	OR (95% CI)	P
None	20(30.8)	40(30.8)		
Both smoking and alcohol consumption	37(56.9)	38(29.2)	1.95(0.96-3.93)	0.063
Consumption of alcohol alone	5(7.7)	50(38.5)	0.20(0.07-0.58)	0.003
Smoking alone	3(4.6)	2(1.5)	3.00(0.46-19.43)	0.249

CHAPTER FIVE

DISCUSSION

5.1 Discussion

With the increasing rate of adoption of different lifestyles and cultural trends in developing countries, there has been a concurrent change in both tobacco smoking and alcohol consumption trends leading to concerns on the possible impact of these practices on oropharyngeal cancer epidemiology in Kenya. The purpose of this study was to systematically describe the link between tobacco and alcohol consumption in cases presenting at KNH with oropharyngeal cancer. In addition, there is paucity of data on alcohol and tobacco consumption as risk factors for OPSCC locally.

The finding of the sample characteristics conforms to those documented in both local and international literature. Majority of the cases recruited in this study were found to be predominantly elderly men in their seventh decade of life. According to KDHS 2014, alcohol consumption and tobacco smoking was more common in males as compared to females and in addition, increased consumption was noted amongst the elderly group [37]. The role of tobacco and alcohol in tumorigenesis of head and neck cancers has been recognized for a long time now. One can then postulate in combination with information that it is not surprising that a higher male prevalence was noted in this study.

OPSCC was staged according to TNM classification and further stratified into prognostic stages that range from I-IV. Of the cases recruited, majority presented already in advanced disease (87.7%). According to work published by Onyango and Macharia [38] on deficits resulting to advance disease presentation of head and neck cancers in KNH, failure of the referral system was noted to be a major contributor. This can only be postulated to be the reason for the advance disease most recruits were at presentation; however, this was not assessed in this study.

As expected, multiple oropharyngeal sub-sites were already involved at presentation. The tonsillar complex was the most frequent sub-site involved (60%) in this study.

The majority of tumors were well differentiated. This was also noted in retrospective cohort analysis carried out over 3 decades by Mehta V. et al in which they found that most OPSCC

were well differentiated. However, there was decline over time of incidence of well differentiated tumors. This decrease in tumor differentiation was attributed to influence of human papillomavirus in OPSCC. HPV induced SCC typically display non/poorly keratinization differentiation. HPV status was not assessed in this study and its influence cannot be ruled out. An ongoing study by Aswani J. on high risk HPV in head and neck squamous cell carcinoma locally will further give impact of HPV status on head and neck cancers. No association was noted between the disease stage and histologic grading.

As expected the prevalence of lifetime smoking was higher among cases (61.5%) compared to controls (30.8%).The analysis showed that 28.3% of the burden of oropharyngeal cancer was attributable to tobacco smoking. The increase in risk of oropharyngeal carcinoma that was attributed to smoking in the population was 34.8% implying a 34.8% reduction in the risk of oropharyngeal SCC in the population if smoking was eliminated. This study confirms findings in other studies that have demonstrated similarly strong associations between tobacco smoking and oropharyngeal cancer [23, 24, and 26].

The prevalence of alcohol consumption was 64.6% among the oropharyngeal carcinoma cases compared to 67.7% among the controls. However, higher levels of alcohol consumption were noted amongst the cases compared to the controls.

Being a current smoker was associated with a five-fold increase in the odds of OPSCC. Rajesh P et al reported higher odds of 7.1, and this higher risk being explained by the different tobacco consumption habits that were practised in India[22]. Cessation of smoking was noted to have reduced risk for oropharyngeal cancer. Participants who had quit smoking had a two to three-fold increase in risk of SCC compared to non-smokers, however compared to the current smokers; a decrease of risk was appreciated. Similar trend was noted by Blot W. Et al[23] in which reducing risk occurred with increasing smoking cessation period.

Alcohol consumption in this study did not have a significant association with OPSCC (OR = 0.87, 95% CI 0.47 – 1.63, p = 0.668). However, an increase in alcohol consumption was noted to have a directly proportional increase in risk of OPSCC. Similar dose related trend has been reported in studies such as Blot W et al [23]. In this study, heavy alcohol consumption was associated with five times higher odds of OPSCC (OR = 5.22, 1.80 – 15.12) as compared to

participants who did not consume alcohol. Altieri et al [27] demonstrated that the odds ratio for oral and pharyngeal cancers were directly proportional to the increasing level of alcohol consumption.

Most studies have demonstrated synergistic effects of joint exposures of alcohol and tobacco smoking[23,24]. A similar study done on causation of alcohol consumption and tobacco smoking on laryngeal squamous cell carcinoma at the Kenyatta National Hospital also demonstrated synergism [(39).] In this study, surprisingly, synergism was not noted. As previously mentioned, tobacco smoking was noted to have a stronger association to OPSCC as compared to alcohol consumption. With joint exposure as compared to tobacco smoking, the risk reduces from 3 to 1.95. Alcohol consumption amongst the participants varied greatly. The type of alcohol constituted beers, hard liquor, wine and traditional brews. The composition of the traditional brews is unknown and they differ from one culture to another. The effects of the constituents of the brews are thus unknown and further evaluation and analysis is needed to find out if they confer a protective aspect.

In addition, the controls selected were from the orthopaedic unit in which most admissions are alcohol related and thus this would thus result in a higher prevalence of alcohol amongst the controls.

5.2 Conclusion

In summary, this hospital based case control study strongly implicates tobacco smoking as a major determinant of oropharyngeal squamous cell carcinoma. Alcohol consumption had a contributory factor in OPSCC development. No synergism is noted with joint exposures.

Most patients were in advanced disease at time of presentation and multiple subsites involved.

5.3 Recommendations

Measures to prevent OPSCC should be aimed at reducing intake of both alcohol and tobacco smoking.

Stringent measures by the government to ensure the Tobacco control bill 2012[40] and Alcoholic drinks control Act, 2012[41] are adhered to, with an aim of reducing prevalence of cigarette smoking and alcohol consumption.

Cancer Prevention and Control Act Cap 246B [18] needs to be executed so that an effective a National Cancer registry Institute is developed.

There should be public health awareness of symptomatology of OPSCC and continuous health care education to ensure early detection and management. There should be development and implementation of proper referral systems for prompt diagnosis and treatment.

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APPENDICES

APPENDIX 1: NIAAA Classification of drinking patterns

Classification of alcohol drinking pattern (drinks per week)

	Female/week	**Male/week**
Non drinkers	Nil	Nil
Light	≤3drinks	≤3drinks
Moderate	3-7drinks	3-14drinks
Heavy	7-14drinks	14-21drinks
Very heavy	>14drinks	>21drinks

Adapted from Nation Institute of Alcohol abuse and alcoholism (NIAAA)

APPENDIX 2: AJCC TNM CLASSIFICATION OF OROPHARYNGEAL CARCINOMA

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tcis	Carcinoma in situ
T1	Tumor =2cm in greatest dimension
T2	Tumor >2cm but not more than 4cm in greatest dimension
T3	Tumor >4cm in greatest dimension or extension to lingual surface of the epiglottis
T4a	Moderately advanced, local disease • Tumor invades the larynx, deep/extrinsic muscle of the tongue, medial pterygoid, hard palate, or mandible
T4b	Very advanced, local disease • Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases the carotid artery
Regional lymph nodes (N)	
Nx	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
Ncis	Carcinoma in situ
N1	Metastasis in a single ipsilateral lymph node =3cm in greatest dimension
N2	Metastasis in a single ipsilateral lymph node >3cm but not more than 6cm in greatest dimension; or in multiple ipsilateral lymph nodes, none >6cm in greatest dimension; or in bilateral or contra lateral lymph nodes, none >6cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node >3cm but not more than 6cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none >6cm in greatest dimension
N2c	Metastasis in bilateral or contra lateral lymph nodes, none >6cm in greatest dimension
N3	Metastasis in a lymph node >6cm in greatest dimension
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Stage grouping

O	**Tis**	**N0**	**M0**
I	**T1**	**N0**	**M0**
II	**T2**	**N0**	**M0**
III	**T1**	**N1**	**M0**
	T2	**N1**	**M0**
	T3	**N0**	**M0**
IVA	**T4**	**N0**	**M0**
	Any $T_{1,2,3}$	**N2**	**M0**
IVB	**Any $T_{1,2,3}$**	**N3**	**M0**
IVC	**Any T**	**Any N**	**M1**

APPENDIX 3: GENERAL PATIENT INFORMATION AND CONSENT FORM

My name is Dr. Grace Mwangi, a resident doctor in ENT Head and Neck surgical unit and principal researcher in this study, which has been approved by the KNH/UON Ethical and research committee.

BACK GROUND

I aim to find out how widespread is cancer of the back of the throat is and risk associated with alcohol consumption and tobacco smoking at KNH. A study has been done on the effect of alcohol and tobacco smoking in cancer of the voice box in the ENT unit and it was noted that they increase the risk of developing the cancer. I am researching to find out if this is the same when it comes to cancer of the back of the throat.

STUDY PROCEDURES

Once you consent for your participation, I will ask you questions regarding the risk factors that have been associated with the illness and using information from your medical records, also retrieve further information on the type of cancer and the site affected.

VOLUNTARINESS OF PARTICIPATION

Participation in this study is voluntary. Once inducted in the study, you can choose to discontinue at any time.

CONFIDENTIALITY

The study will not reveal your identity and all information will be handled with utmost privacy.

BENEFITS

The information we get may not be of immediate benefit to you but it will help doctors to understand further the illness and its risk factors. The findings like all scientific information will be published in scientific journal or presented in scientific conferences without divulging specific patient information.

RISKS

There are no risks or extra cost that you will incur.

RIGHTS TO WITHDRAW

It is not compulsory to participate in this study. You are free to decline participation in the study and there will be no discrimination towards you. All patients will receive the same management irrespective of whether they participate in the study or not.

In case of any further queries, feel free to contact the following for clarification:

1. **Principal Investigator**

Dr. Grace Mwangi

O720361455

2. **Supervisors**

PROF. HERBERT OBURRA, MB, MMED (Nbi), FRCS-Edin (OTO)
PROFESSOR, DEPARTMENT OF SURGERY, UNIVERSITY OF NAIROBI
0722516675

DR. CATHERINE IRUNGU, MBChB, MMED (ENT)
CONSULTANT ENT SURGEON, LECTURER, DEPARTMENT OF SURGERY, UNIVERSITY OF NAIROBI
0722385710

3. **The Chairperson**,

KNH/UON ERC,

Kenyatta National Hospital

Tel. No. +2542726300 Ext 44102

If you fully understand everything and are willing to participate, kindly sign the consent form provided.

CONSENT FORM

Study number.....

I .....do herby consent to enrol self/my child/Mr/Mrs/..... to be included in this study on "SMOKING AND ALCOHOL INGESTION AS RISK FACTORS FOR OROPHARYNGEAL SQUAMOUS CELL CARCINOMA" to me by Dr. Grace Mwangi.

I also confirm I that no monetary or material gains have been promised or given to me for participation in this study.

Signed..... Date.....

Signed (Doctor)..... Date.....

1. **Principal Investigator**

   Dr. Grace Mwangi

   0720361455

2. **Supervisors**

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   Professor, Department Of Surgery, University Of Nairobi
   0722516675

   Dr. Catherine Irungu, Mbchb, Mmed (Ent)
   Consultant Ent Surgeon, Lecturer, Department Of Surgery, University Of Nairobi
   0722385710

3. **The Chairperson**,
   KNH/UON ERC,

   Kenyatta National Hospital

   Tel. No. +2542726300 Ext 44102

APPENDIX 4: KIAMBATISHO: MAELEZO YA UTAFITI NA KUHUSU IDHINI YA MGONJWA

Jina langu ni Daktari Grace Mwangi, mtafiti mkuu kwa utafiti huu ambao unachunguza ikiwa uhusiano baina ya uvutaji wa sigara na unywaji wa pombe unachangia kwa uambukizi na saratani ya oropharynx. Kushiriki kwa utafiti huu ni kwa hiari yako. Lengo letu kwa kufanya utafiti huu ni kutuwezesha kutathmini idadi na jinsi vile unywaji pombe na uvutaji wa sigara zinazochangia kwa hii saratani katika Hospitali kuu ya Kenyatta.

Maelezo ya taratibu ya utafiti huu
Baada ya kukubali kushiriki na utafiti huu, utaulizwa maswali kuhusu mambo yanayolengwa na saratani hii pamoja na kuchambua rekodi zako za hospitali tutaweza pata taarifa kuhusu saratani. Taarifa zote tunazozipata zitawekwa faraghani.

Je, kuna hatari yoyote kwa kushiriki katika utafiti huu?
Hakuna hatari yo yote itakayosababishwa na utafiti huu wala gharama yoyote zaidi watakayotozwa washiriki. Uko na uhuru wa kutoshiriki kwa utafiti huu na utashughulikiwa sawa na watakaoshiriki bila adhabu yeyote.

Ni faida gani nitakayopata kwa kushiriki?
Hakuna faida ambayo utapata kwako, iwe pesa taslimu au fidia yoyote. Lakini matokeo ya utafiti huu yatasaidia madaktari kuelewa chanzo cha saratani hii na vipi matibabu yake yanaweza kuboreshwa zaidi. Kuna uwezekano wa kuchapishwa kwa matokeo ya utafiti huu katika majarida ya kisayansi au kuwekwa kwa mikutano ya kisayansi na hata kwa gazeti ya kawaida ili kuwezesha kila mtu husika kufaidika na matokeo yoyote ile.

Kwa maelezo zaidi, unaweza kujadiliana na walio orodheshwa hapa chini:

1. Mtafiti Mkuu:
   Daktari Grace Mwangi
   Rununu: 0720361455

2. Wasimamizi:
   Prof. Herbert Oburra, Mb, Mmed (Nbi), Frcs-Edin (Oto)
   Professor, Department Of Surgery, University Of Nairobi
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   Dr. Catherine Irungu, Mbchb, Mmed (Ent)
   Consultant Ent Surgeon, Lecturer, Department Of Surgery, University Of Nairobi. 0722385710

3. Mwenyekiti,
   Knh/Uon Erc,
   Hospitali Ya Kitaifa Ya Kenyatta,
   Simu: +2542726300 Ext 44102

Kama umeridhika na mambo haya yote, na ukiwa tayari kushiriki, tafadhali weka sahihi yako kwenye fomu ya idhini.

FOMU YA IDHINI

Nambari ya utafiti .....

Mimi .....nakubali mimi/mwanangu ninayemsimamia .....kushiriki katika utafiti huu ambao nimeelezewa kikamilifu na Daktari Grace Mwangi. Nathibitisha pia ya kwamba sijapewa au kuahidiwa pesa taslimu, fidia au chochote kile, kushiriki kwenye utafiti huu.

Sahihi ..... Tarehe.....

Sahihi (mtafiti)..... Tarehe.....

1. Mtafiti Mkuu:

   Daktari Grace Mwangi

   Rununu: O720361455

2. Wasimamizi:

   Prof. Herbert Oburra, Mb, Mmed (Nbi), Frcs-Edin (Oto)
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APPENDIX 5: STUDY PROFORMA (CASES)

STUDY NUMBER ☐

AGE IN YEARS ☐

SEX: MALE ☐ FEMALE ☐

REGION/COUNTY OF ORIGIN_____

OCCUPATION _____

HAS THE PATIENT EVER SMOKED? ☐ NO ☐

DURATION OF SMOKING _____

QUANTITY SMOKED PER DAY _____ CALCULATED PACK YEARS _____

IF QUIT SMOKING, HOW LONG AGO?_____

HAS THE PATIENT EVER CONSUMED ALCOHOL? ☐ NO ☐

TYPE OF ALCOHOL:

BEER ☐ WINE ☐ SPIRIT ☐ OTHER ☐

AMOUNT OF DRINKS PER DAY _____

NUMBER OF TIMES OF CONSUMING ALCOHOL IN A WEEK _____

TUMOR CHARACTERISTICS

HISTOLOGY	TICK WHERE APPLICABLE
WELL DIFFERENTIATED	
MODERATELY DIFFERENTIATED	
POORLY DIFFERENTIATED	
UNDIFFERENTIATED	

TUMOR STAGING =.....

SUBSITE

Soft palate and uvula	
Palatine tonsils and tonsillar fossa	
Base of tongue	
Vallecula	
Lateral and posterior oropharyngeal walls	

APPENDIX 6: STUDY PROFORMA (Controls)

STUDY NUMBER ☐

AGE IN YEARS ☐

SEX: MALE ☐ FEMALE ☐

REGION/COUNTY OF ORIGIN _____

OCCUPATION _____

HAS THE PATIENT EVER SMOKED? ☐ NO ☐

DURATION OF SMOKING _____

QUANTITY SMOKED PER DAY _____CALCULATED PACK YEARS _____

IF QUIT SMOKING, HOW LONG AGO? _____

HAS THE PATIENT EVER CONSUMED ALCOHOL? YES ☐ NO ☐

TYPE OF ALCOHOL:

BEER ☐ WINE ☐ SPIRIT ☐ OTHER ☐

AMOUNT OF DRINKS PER DAY _____

NUMBER OF TIMES OF CONSUMING ALCOHOL IN A WEEK

DURATION

IF QUIT DRINKING, HOW LONG AGO? _____