DETERMINATION OF THE CHARACTERISTICS AND POSSIBLE RISK FACTORS ASSOCIATED WITH SQUAMOUS CELL CARCINOMA OF THE HYPOPHARYNX AT KENYATTA NATIONAL HOSPITAL

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A Proposal for a dissertation to be submitted in part fulfilment of the requirements for the Degree of Masters of Medicine in Ear, Nose and Throat Surgery, University of Nairobi

DECLARATION

I declare that this dissertation is my original work and that it has not been submitted for a degree award in any university.

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This dissertation has been submitted for the degree of Master of Surgery in ENT-HN Surgery with my approval as a university supervisor.

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ACRONYMS AND ABBREVIATIONS

AJCC	-	American Joint Commission on Cancer
ENT-HN	-	Ear, Nose and Throat-Head and Neck
HC	-	Hypopharyngeal Cancer
HNC	-	Head and Neck Cancer
HNSCC	-	Head and Neck Squamous Cell Carcinoma
IQR	-	Inter-Quartile-Range
KNH	-	Kenyatta National Hospital
LC	-	Laryngeal carcinoma
M-EC	-	Mid-esophageal cancer
OR	-	Odds Ratio
PAH	-	Polycyclic Aromatic Hydrocarbons
SD	-	Standard deviation
UADT	-	Upper Aerodigestive tract
UICC	-	International Union Against Cancer

ABSTRACT

Introduction:

Head and neck cancer has been on the increase in the last few decades. Just as well hypopharyngeal carcinoma cases are increasing and patients younger than described in most literature are being diagnosed with the disease. Patients presenting with hypopharyngeal carcinoma at Kenyatta National Hospital (KNH) are diagnosed at advanced stage of the disease due to late presentation. This is partly because of lack of awareness of symptoms and also lack of knowledge on the risk factors that predispose patients to developing hypopharyngeal cancer.

Objectives: To determine the characteristics and possible risk factors in patients with squamous cell carcinoma of the hypopharynx at Kenyatta National Hospital.

Study Design: A hospital based descriptive cross – sectional study.

Study setting: The study was carried out at KNH in the Ear, Nose and Throat ward and out-patient clinic, as well as the radiotherapy department. This was done after ethical approval from the KNH-University of Nairobi research and ethics committee.

Study population: All patients over the age of 12 years with confirmed hypo pharyngeal carcinoma who gave consent and assent form for the study from the ENT clinic, ENT ward, and radio-therapy department. Sixty nine cases were recruited for the study.

Methodology: The study was carried out between August 2013 and January 2014. The patients' demographic data, medical history and physical examination findings were recorded in a patient proforma. The characteristics and possible risk factors in each patient were obtained by means of a questionnaire.

Results: Mean age was 50.6years (SD = 15years) with majority 41(59.4%) being male. Majority of the patients presented in the 6^{th} and 7^{th} decade with 21(30.4%) and 16(23.1%) patients respectively. Dysphagia was present in 69(100%). Seventeen (24.6%) of the patients were exposed to farming chemicals with a mean duration of 30years of exposure. Use of water direct from the river was common in 66.6% of the patients. Smoking was present in 36(52.1%) patients and all were male with the

commonest type being filtered cigarettes, 32(87.8%). Secondary smoke exposure in 15(23.8%). Alcohol consumption was present in 35(50.7%) of patients 30(93.8%) of which also smoked. Intake of fruits and vegetable was low among the patients. The most common histologic was moderately differentiated SCC with the postcricoid region being the most affected subsite.

Conclusion and recommendation: More studies need to be done to evaluate the real risk of certain environmental exposures as well as exposure to smoking, alcohol consumption and farming chemicals in areas most affected.

1. INTRODUCTION

Head and Neck cancer includes cancers that arise from the upper aerodigestive tract. This typically refers to head and neck squamous cell carcinoma (HNSCC). In the last few decades the incidence of HNSCC has been on the increase. HNSCC forms five to fifty per cent of all cancers globally[1]. HNSCC is the sixth most common cancer in the world, with about half a million new cases diagnosed anually.[2] There has been a well established association between the development of HNSCC and the use of alcohol and tobacco.[3] Other factors associated with head and neck cancer are genetic factors, nutritional deficiencies and oncogenic virus infections[4]. There has been a steady increase in cancer of the head and neck (HNC) in Kenya[5]. The rates in males have increased from 10.8% in 2000, 14.1% in 2001, to 19.1% 2002. In females the rate increased from 5.1% in 200 to 6.9% in 2001 and 8.7% in 2002[5]. Hypopharyngeal carcinoma is one of the common head and neck cancers encountered at the Kenyatta National Hospital (KNH) ENT clinic. It tends to have a late presentation due to the site of tumour. Patients with hypopharyngeal carcinoma also tend to have the worst prognoses in all head and neck cancers. This is due to the fact that the disease tends to have submucosal spread that can be extensive, also early regional lymph node involvement and a tendency to early distant metastasis[6].

2. BACKGROUND

2.1 ANATOMY OF THE HYPOPHARYNX

The hypopharynx is divided into 3 parts by International Union Against Cancer (UICC) in 1997[7]:

UICC classification

1. Pharyngo-oesophageal junction (postcricoid area) extends from the level of the arytenoid cartilages and connecting folds to the inferior border of the cricoid cartilage, thus forming the anterior wall of the hypopharynx
2. Pyriform sinus extends from the pharyngoepiglottic fold to the upper end of the esophagus. It is bounded laterally by the thyroid cartilage and medially by the hypo pharyngeal surface of the aryepiglottic fold and the arytenoids and cricoid cartilages

3. Posterior pharyngeal wall extends from the superior level of the hyoid bone (or floor of the vallecula) to the level of the inferior border of the cricoid cartilage and from the apex of one piriform sinus to the other

The hypopharyngeal mucosa consists of stratified squamous epithelium of the non-keratinizing type. The pyriform sinuses have a rich underlying lymphatic network, this is less extensive in the other subsites. The lymphatic drainage from the pharynx is into levels IIb, III, IV cervical lymph nodes and retropharyngeal nodes[8].

2.2 HYPOPHARYNX CARCINOMA

Historically tumours of the hypopharynx were considered as extrinsic carcinomas of the larynx. Even though the larynx and the hypopharynx are in close proximity of each other, the natural history of the tumours arising from these sites could not be more dissimilar with hypopharyngeal cancer being associated with less than half the survival rate of its laryngeal neighbour. The primary pathology encountered is squamous cell carcinoma (SCC), which usually presents at an advanced stage and thus poses several challenges to the managing physician. Of the SCC, 70% are moderately to well differentiated histologically.

Other histological types of hypopharyngeal carcinoma are[9]:

- Basaloid squamous carcinomas.
- Spindle-cell (i.e., sarcomatoid) carcinomas.
- Small-cell carcinomas.
- Nasopharyngeal-type undifferentiated carcinomas (i.e., lymphoepitheliomas).
- Carcinomas of the minor salivary glands

In the United States and Canada, 65% to 85% of hypopharyngeal carcinomas involve the pyriform sinuses, 10% to 20% involve the posterior pharyngeal wall, and 5% to 15% involve the postcricoid area[10]. Hypopharyngeal carcinomas tend to spread within the mucosa, beneath intact epithelium and thus can have skip lesions occurring far the from primary tumour. And for this reason and the fact that there is a rich lymphatic network within the hypopharynx, a localized tumour is an exception[11].

2.3 RISK FACTORS FOR HYPOPHARYNGEAL CARCINOMA

The causal relationship between alcohol and tobacco intake, genetic predisposition, diet, and socioeconomic conditions in the development of squamous cell cancers of the head and neck applies as well to hypopharyngeal cancer[12].

2.3.1 Smoking

Cellular DNA constantly encounters various endogenous and exogenous damaging agents some of which are carcinogens. Cigarette smoking is a major cause of head and neck cancer[13]. The carcinogenic compounds in cigarette smoke may exert their effects either without modification or by first being degraded or metabolized to active carcinogens. There are 55 mutagenic compounds that have been identified in tobacco smoke, and these include aromatic heterocyclic compounds and epoxides[14]. Polycyclic aromatic hydrocarbons (PAH) are the better known carcinogens and benzo(a)pyrene is the representative compound that has been studied extensively in carcinogenetic models for lung cancer both in animals and humans. PAH are formed as products of incomplete combustion of tobacco. Once absorbed, they are oxidized via mixed function oxidase enzyme systems, cytochrome P450 enzymes to form oxides and epoxides[15]. The epoxide formed is then hydrolysed into dihydrodiol. The dihydrodiol formed is then either conjugated with glutathione, glucuronic acid or sulphate in order to be excreted and they are rendered harmless. However, it can also be further oxidized through a similar cytochrome P450 enzyme system to form further classes of epoxides. The epoxide formed is a potent electrophilic substance that reacts readily with proteins, RNA and DNA. In case of DNA, it has a higher affinity to form covalent bond with guanine especially at the 0-6 position. The covalently bonded (alkylated) DNA can then be repaired through cell cycle mechanisms to restore normal DNA or be replicated as an adduct leading to mutations and, therefore, neoplastic transformation[16]. The upper aerodigestive tract (UADT) has low repair ability for PAH induced DNA damage, hence DNA adducts persist setting stage for mutation and finally carcinogenesis [17].

Other polycyclic aromatic compounds besides PAH act in a similar manner. Aromatic amines (AA) like 2-nathylamine which are transformed into electrophilic intermediates through various enzyme systems including cytochrome P450 that then bond DNA to form adducts. Similarly, nicotine through a process of nitrosation after absorption into the body forms tobacco specific nitrosamines: N-nitrosonornicotine (NNN), and 4-(methyinitrosamino)-1-(3-pyridyl)-1-butanone (NNK). NNN and NNK are strong carcinogens and they exert their effect by hydroxylation and formation of electrophilic intermediates like methyl diazohydroxide which will again react with DNA giving rise to methylated DNA (e.g. 7-methylguanine) which enhance miscoding in DNA replication[18]. Replication of the DNA and subsequent proliferation of the cells are prerequisites for the

development of neoplasms[19]. Persistence of the DNA lesion in an adduct may result in genetic alterations during replication, e.g. base substitution, such as replacing a guanine with a cytosine. Various types of chromosomal damage or anomalies can then result during replication such as chromosomal translocation, recombination and gene amplification.

Glutathione S-transferase (GST) is a family of enzymes that are responsible for detoxification of such harmful substances. However, there are five different loci for its production of subtypes of GTS and these subtypes have various pleomorphism. Also variation in Uridine 5-diphospo-glucoronosyltrnasferace has been implicated in increased risk on head and neck cancer[19]. A low-activity UGT genotype was associated with 3.7-fold greater odds of developing laryngeal cancer in smokers; the odds ratio increased to 6.1 in heavy smokers and was not increased in those who never smoked[20].

2.3.2 Alcohol

Approximately 3.6% of cancers worldwide are derived from chronic alcohol drinking, including upper aerodigestive tract, liver, breast, and colon[21]. Heavy alcohol consumption has been associated with a higher risk of development of hypopharyngeal cancer compared to laryngeal cancer (e.g. supraglottic or glottis)[22]. Alcohol consumption has been related to damage of the mucosa of the upper aerodigestive tract (UADT). This is thought to then allow the absorption of other carcinogens such as from tobacco smoke[23]. Alcohol is rapidly metabolized to acetaldehyde, the first metabolite of ethanol, by mucosal and cellular alcohol dehydrogenase, cytochrome P4502E1 and through bacterial oxidation[24]. Acetaldehyde which has similar chemical backbone as formaldehyde, a known carcinogen, causes DNA damage by attaching to DNA and forming DNS adducts. Alcohol is a known solvent of tobacco carcinogens leading to increased absorption of tobacco carcinogens in UADT[17]. Alcohol has been shown to also reduce the activity of DNA repair enzymes and increase chromosomal damage through inhibition of DNA methylation and interacting with retinoid metabolism at cellular level[25]. Recent studies in Asia have also shown that up to 30% of Japanese have a mutation on the acetaldehyde dehydrogenase gene, and thus have an increased risk of UADT cancer[26].

Maier et al[27] showed that chronic alcohol use may up-regulate enzymes of the cytochrome-P450 system, which in turn activate procarcinogens to carcinogens. This is a critical step as most environmental carcinogens exist in their procarcinogenic form. Alcohol also interferes

with metabolism of vitamin A[28]. Retinol is oxidized to retinoic acid which is important in controlling cell growth, differentiation, and apoptosis. So alcohol causes increased metabolism of vitamin A by CYP450 thus inducing carcinogenesis[28].

2.3.3 Diet

It is becoming clearer as research continues that nutrition plays a major role in cancer. It has been estimated by the American Institute for Cancer Research and the World Cancer Research Fund that thirty to forty percent of all cancers can be prevented by appropriate diets[29]. Vitamin deficiency has been linked to development of head and neck cancer. Vitamin A has been shown to control cell differentiation and thus able to inhibit development of epithelial tumors[30]. Epidemiological data suggests a protective role of dietary carotenoids and an inverse association between the consumption of fruit and vegetables and the incidence of head and neck cancer[31]. Deficiencies in folic acid and zinc have been shown to contribute to enhanced tobacco carcinogenesis among chronic alcoholics due to loss of folic transmethylation that regulates gene expression[31]. This is because folic acid, as well as Vitamin B12 plays an important role in DNA methylation as co-enzymes in the pathway for synthesis of methionine and S-adenosyl methionine which is a methyl donor[32].

2.3.4 Plummer-Vinson Syndrome

Iron deficiency anemia, in association with glossitis, esophageal webs, koilonychias and dysphagia make up the Plummer-Vinson syndrome which has been linked to postcricoid carcinoma of the hypopharynx[33]. This syndrome was first described in the United States in 1922 by Plummer and Vinson, then later by Patterson and Kelly[34]. The link between the symptoms and syndrome is not clear but it is thought that the anemia is responsible for the development of dysphagia. This thought to be due to mucosal changes that occurs as a result of the iron deficiency and chronic mucosal irritation by retained food[35]. Ahlbon[36] was the first to document the relation between the syndrome and hypopharyngeal cancer in 1936. It is associated with a 10% risk of developing hypopharyngeal or oesophageal cancer[37]. The cancer will appear in a region where the mucosal changes are distinct in a patient with Plummer-Vinson syndrome.

2.3.5 Occupational

People working in the metal industry, construction, ceramic industry, food industry, coal mines, and lumber industry have been found to have an increased risk of hypopharyngeal SCC as seen in a few case control studies[38]. Exposure to asbestos, carbon and formaldehyde has also been implicated[39]. Formaldehyde is rapidly metabolized by glutathione-dependent formaldehyde dehydrogenase (also known as alcohol dehydrogenase 5, ADH5) and *S*-formyl-glutathione hydrolase to formic acid, which enters the one-carbon pool and can be either excreted in the urine or oxidized to carbon dioxide and exhaled[40]. Formaldehyde exposure is associated with key events related to carcinogenicity, such as DNA reactivity, gene mutation, chromosomal breakage, aneuploidy, epigenetic effects (binding to lysine residues of histones), glutathione depletion, oxidative stress, and cytotoxicity-induced cellular proliferation[41]. In addition, levels of formaldehyde-DNA adducts in leukocytes were significantly higher in smokers than in non-smokers. However, it is not known whether the source of the adducts was formaldehyde in tobacco smoke or from the metabolism of a tobacco-specific compound[42]. There are basically three hypotheses regarding the pathogenesis of asbestos-induced DMM, which may be summarized as follows[43]:

(1) The “oxidative stress theory” is based on the fact that phagocytic cells that engulf asbestos fibres produce large amounts of free radicals due to their inability to digest the fibres, and epidemiological studies indicating that iron-containing asbestos fibres appear more carcinogenic.

(2) The “chromosome tangling theory” postulates that asbestos fibres damage chromosomes when cells divide; and

(3) The “theory of adsorption of many specific proteins as well as carcinogenic molecules” states that asbestos fibres *in vivo* concentrate proteins or chemicals including the components of cigarette smoke.

2.3.6 Genetics

Loss of homeostatic control of cell growth and death has been shown to cause the development of head and neck cancer, and this can be genetically determined. There are about forty proteins that control the cell cycle in the body. These are products of proto-oncogenes and tumour suppressor genes. Mutation of these genes creates an imbalance with activation of proto-oncogene and tumour suppressor gene inactivation. The accumulation of these alterations underlies the progress from a normal cell to a cancerous one, a process

referred to as multistep carcinogenesis. It is estimated that about six to eleven such genetic alterations are required for the development of HNSCC[44].

2.4 EPIDEMIOLOGY

The incidence of hypopharyngeal carcinoma varies with geographic location. Epidemiological data on hypopharyngeal carcinoma has been scarce. Two major retrospective studies in the United States help shed some light on the epidemiology of this cancer in that country. Canto and Devesa[45] analysed data from 1975 to 1988 in nine different registries in the Surveillance, Epidemiology and End Results (SEER) database. They found an incidence of 0.4-0.9% for hypopharyngeal carcinoma in white males, 0.8 – 2.3% in black males, 0.2% for white females, and 0.2 – 0.5% for black females. Hoffman et al[46] conducted a second retrospective study by analysing the National Cancer Data Base (NCDB), which is a hospital based registry. They analysed cancers registered from 1985 to 1994. They found that cancer of the hypopharynx composed 4.3% of all head and neck cancer. 95% were squamous cell carcinoma, the remainder having been adenocarcinoma, lymphoma and other pathologies. 77.3% were Stage III and IV tumour demonstrating the late stage at presentation. The 5-year survival rate was 31.4%. In the USA, approximately 2,500 patients are diagnosed with hypopharyngeal carcinoma each year[8]. In the same study by Hoffman et al[46] hypopharyngeal carcinoma was found to form 0.5% of all malignancies with an incidence of 1 per 100,000 population, and affecting men more than women. In the Netherlands, review of data between 1989 and 2001 revealed that 0.23% of all new head and neck cancer were hypopharyngeal carcinoma. Hypopharyngeal cancers during that period were found to be 6.7% of all head and neck cancers which was thought to have been comparable to North-west Europe and North America[47]. The reported male to female ratio was 1.3:1 to 2.1[48,49].

2.5 MANAGEMENT

2.5.1. History

The cardinal symptoms of hypopharyngeal cancer are progressive dysphagia, unilateral otalgia, chronic sore throat, hoarseness of voice and weight loss. Pain on swallowing and globus sensation should also raise suspicion. Otalgia is due to referred pain through a branch of the Vagus nerve, Arnold's nerve that supplies the mucosa of the piriform sinus, supraglottis and post cricoids region, which also supplies sensation to the external auditory

canal. Also the Jacobson's nerve a branch of glossopharyngeal nerve will cause otalgia through referred pain from the base of tongue mucosa in high piriform sinus tumour through its supply to the middle ear mucosa. Postcricoid tumour presents early due to dysphagia, while piriform fossa tumour presents late mostly. Hoarseness is due to either cricopharyngeaus muscle, invasion of cricoarytenoid joint, invasion of recurrent laryngeal nerve, or hemilarynx fixation through paraglottic invasion. Those that arise from the medial wall of the piriform are more extensive than they clinically appear. 75% of patients will present with unilateral cervical lymphadenopathy, while 5% will present with bilateral lympadenopathy[8].

2.5.2 Diagnosis

Diagnosis of hypopharyngeal cancer is made after a detailed history and thorough physical examination which includes specific ENT H&N clinical examination such as indirect mirror laryngoscopy. Specialized imaging usually CT scan of the head and neck is performed, then subsequent endoscopy and biopsy.

2.5.3 Physical examination

Most patients are in their seventh decade[8]. General ENT H&N examination is carried out with special attention to the neck for any swellings. Fixation of the hemilarynx occurs in half the cases with piriform fossa cancer. Indirect mirror laryngoscopy is usually done to visualize the hypopharynx and in some patients pooling of saliva is seen in the piriform sinus (Chevalier Jackson's sign). Trotter's sign (loss of laryngeal crepitus) is often seen in large tumours of the postcricoid region. Flexible nasopharyngoscopy should be performed where possible and there after a formal endoscopy under anaesthesia should be done and a biopsy for histological diagnosis obtained.

2.5.4 Imaging Studies

Contrast-enhanced CT scans obtained with appropriate section thickness aid in the evaluation of cancer. CT scans and MRIs can demonstrate the extension of the tumour into vital structures such as the surrounding soft tissue and, therefore, aid in staging of the lesion

Plain radiography of the chest will provide information on the presence of lung metastasis.

PET-CT scan is a radiologic tool that detects metabolic signals from cells with high metabolic activity like cancer cells. This is the most sensitive test available to detect metastasis or second primary tumours, though this is not available locally.

CT scan is the best radiological examination to assess the size and extent of the lesion and is necessary in planning for the most appropriate mode of treatment.

2.5.5 Staging

The American Joint Committee on Cancer (AJCC)[50] has designated staging by TNM for hypopharyngeal cancer (Appendix IV: Table 1 – 3).

2.5.6 Treatment

In other centres, approximately 25% of the patients with hypopharyngeal carcinoma are not treatable at presentation due to the advanced stage of the disease as well as advanced age, poor general condition, local tumour inoperability and extensive neck disease[10]. Treatment may include; radiotherapy or surgery. The surgical procedures may be laser and diathermy excision, partial pharyngectomy and total laryngectomy, total pharyngolaryngectomy, total pharyngolaryngoesophagectomy and replacement with stomach transposition, partial pharyngectomy and supra glottis laryngectomy, lateral pharyngectomy of tumours of the lateral pharyngeal wall and transhyoid partial pharyngectomy.

3. LITERATURE REVIEW

There is no reliable cancer registry in Kenya at present which can be used to determine epidemiology of cancer. Cancer as a disease is ranked third as a cause of death in Kenya after infectious and cardiovascular diseases[4]. In the last cancer incidence report of 2005 Mutuma found that head and neck cancer was the most common cancer in males (14.8%), and the third most common in females[5]. At Kenyatta National Hospital hospital, cancer of the larynx was found to have been the most common head and neck cancer followed by nasopharyngeal, hypopharyngeal and oral cancer in a study conducted by Nyandusi in 2007 [Dissertation, University of Nairobi]. Worldwide it has been reported that patients will present in the seventh decade of life[8]. Smoking increases the risk factor for hypopharyngeal carcinoma by a

factor of 2 to 40, while alcohol will increase this risk by a factor of 1.5 to 6 independent of smoking status[51,22].

Wahid et al[48] reviewed (75) patients with diagnosed with hypopharyngeal cancer among whom 92% presented with dysphagia and also majority of the patients were in their seventh decade of life while Bosetti et al[51] in his review of 195 patients had 36-49% of patients in their seventh decade.
In the same study by Wahid et al the male to female ratio was 1.3:1, while in a review by Blot et al[49] on smoking and alcohol in oral and pharyngeal cancer, the male to female ratio was 2:1.

Bosetti et al[51]did a review of 195 patients with oral and pharyngeal cancer and 1113 controls from several multicentered case-control studies. In his review analysis of data was on risk factors for hypopharyngeal carcinoma like alcohol, smoking and diet. The multivariate odds ratio was 4.6 for heavy smokers and 2.7 for cases with high alcohol intake. Vegetables, fruit, β-carotene and wholegrain foods were inversely related to the risk of developing cancer, while butter and retinol directly related to the risk of developing cancer showing that fruits had a protective role against cancer compared to butter and retinol.

Menvielle et al[22] did a case-control study as well which had 201 patients with hypopharyngeal cancer and 282 with laryngeal cancer. The control group had 242 males with non-respiratory cancers. Both cases and control group in this study had the same risk factors, i.e. exposure to cigarette smoke and alcohol. The odds ratios ranged from 1.4 to 5.9 among regular drinkers and from 3 to 44 among current smokers. Risks among ex-smokers were significantly lowered at approximately one-third of those for current smokers[22]. Concurrent use of alcohol and smoking was found to have a synergistic effect on development of cancer [49]. A dose-effect has been demonstrated for both risk factors in a review in Europe of fifty years of data on cancer among doctors [52]. This demonstrated that the longer the years an individual is exposed to alcohol and cigarette smoke the more likely they are to develop cancer,

Takezaki et al[53] conducted a retro-spective study of 346 patients, 62 with hypopharyngeal and 284 with oesophageal carcinoma. Cigarette smoking increased the OR for M-EC, and alcohol

drinking elevated the ORs for all subsites. The OR tends to increase with the number of cigarettes (p= 0.056), and decrease with years after quitting smoking (p=0.006). The ORs for smoking with drinking were multiplicatively greater than those for smoking or drinking in combined cases of HC and EC. In contrast, daily raw vegetable consumption lowered the ORs for all subsites.

Occupational exposure to certain compounds has long been studied to clarify the level of involvement in the development of neoplasia independent of alcohol and tobacco consumption[54]. It has also been demonstrated that workers in rubber industry, etiological agents of asbestosis, sulphuric acid are at an increased risk of both hypopharyngeal and laryngeal cancer. In 2000, Laforest et al[54] studied the risk of developing hypopharyngeal and laryngeal cancer with occupational exposure to coal dust and formaldehyde. They had 497 patients with 201 being hypopharyngeal cancer, 296 controls. They found increased risk of hypopharyngeal cancer more with formaldehyde and coal dust compared to laryngeal cancer. Hypopharyngeal cancer was found to have been associated with exposure to coal dust (OR 2.31, 95% CI 1.21 to 4.40), with a significant rise in risk with probability ($p<0.005$ for trend) and level ($p<0.007$ for trend) of exposure. A significant relation, limited to hypopharyngeal cancer, was found with the probability of exposure to formaldehyde ($p<0.005$ for trend), with a fourfold risk for the highest category (OR 3.78, 95% CI 1.50 to 9.49).

In a study on exposure to asbestos by Berrino at el[38] 203 patients with hypopharyngeal cancer, 315 with laryngeal cancer and 305 controls revealed an OR 1.80 (95% CI: 1.08-2.99) with a significant risk for hypopharyngeal cancer. Exposure to mineral wool was borderline risk with OR 1.55 (95% CI: 0.99-2.41)[38]. Similar increased risk was found on exposure to organic solvents with adjustment to non-occupational variable (smoking, alcohol, and diet) in France, Italy, Switzerland and Spain[43].

Diet has been implicated in the development of hypopharyngeal cancer. In a study in northern Italy by Franseschi et al[55] found that high consumption of maize with heavy drinking (>42drinks/week) was associated with OR of 3.2, 3.3, and 2.8 for oral cavity, pharyngeal, and oesophageal cancers respectively. 282 patients were included with 107 having pharyngeal cancer, 107 with oral cavity cancer and 88 with oesophageal cancer.

There is scarce literature on descriptive studies done on hypopharyngeal carcinoma and the case-control studies will be used as a background to this study.

4. STUDY JUSTIFICATION

In recent years there has been a steady increase in the cancer burden in Kenya. This also applies to those diagnosed with hypopharyngeal carcinoma. In the ENT ward in KNH there are about 4-5 admissions a month of patients with hypopharyngeal carcinoma. Statistics from the health information department at KNH recorded 74 patients admitted with hypopharyngeal carcinoma in 2012. Of these admissions 67% were males. This is different from what had been observed as more female presentation in the ENT ward. Admissions register in the ENT ward indicate a younger age group, <30yrs, are being diagnosed with the disease. As stated earlier in a study done by Nyandusi in 2007 it was the third commonest head and neck cancer in the ENT department after laryngeal and nasopharyngeal carcinomas. A 55% intake of alcohol consumption and smoking was found at KNH in 2006 by Onyango et al[56] in a retrospective descriptive study of patients with head and neck cancer. Currently there is no data available to give an indication of the possible risk factor in patients with hypopharyngeal carcinoma and their characteristics in Kenya.

5. RESEARCH QUESTION

What are the characteristics and risk factors of patients with squamous cell carcinoma of the hypopharynx at Kenyatta National Hospital?

6. OBJECTIVES

6.1 Main objectives

To determine the demographic characteristics of patients with hypopharyngeal carcinoma presenting at KNH and possible associated risk factors.

6.2 Specific objectives

1. To determine the demographic characteristics of patients with hypopharyngeal carcinoma.

2. To determine the prevalence of alcohol consumption and smoking in patients with hypopharyngeal cancer.
3. To determine the possible occupational exposure in patients with hypopharyngeal cancer.
4. To determine the dietary characteristics of patients with hypopharyngeal carcinoma.
5. To determine the possible cancer associated environmental agents in patients with hypopharyngeal cancer.

7. DESIGN

The study design was a descriptive cross-sectional study.

8. STUDY SETTING

The study was carried out in Kenyatta National Hospital (KNH) at the Ear, Nose Throat Head and Neck (ENT-HN) Surgical ward, ENT-HN Surgery outpatient clinic, radiotherapy ward and outpatient clinic.

9. STUDY POPULATION

All patients with confirmed hypopharyngeal carcinoma attending ENT clinic, Radio therapy clinic and those in the ENT ward from August 2013 to January 2014.

9.1 Inclusion criteria

(a) All patients with confirmed diagnosis of SCC on the hypopharynx.
(b) Patients who give consent for the study.

9.2 Exclusion criteria

a) Patients who do not consent for the study
b) Patients with other histological diagnosis other than SCC.
c) Patients without any histological diagnosis.

10. SAMPLE SIZE

The sample size for this study was calculated based on the estimated proportions of Smokers and Alcohol users.

The sample size was calculated using the Cochrane Sample proportion Formula:

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

where n is the sample, Z is the limits of the normal curve, e is the desired level of precision, P is the estimated proportion in the population. For this population, we will estimate Z at 95% level of confidence($Z = 1.96$), P as 35%, and E as 0.03 (3%) from the prevalence estimate for smokers while P as 30%, and E as 0.03 (3%) from the prevalence estimate for Alcohol drinkers. The total number of patients admitted to KNH with hypopharyngeal carcinoma in 2012 was 74.

The sample size required will be:

Sample size based on Smoking status

$$n = \frac{1.96^2 \times 0.35(1-0.35)}{0.03^2}$$

$$n = 971$$

Adjusting for the Finite Population Correction (FPC) factor we get final sample size $'n$:

$$'n = \frac{n}{1 + {}^{n}/_{N}} = \frac{971}{1 + {}^{971}/_{74}} = 68$$

Sample size based on Alcohol Use

$$n = \frac{1.96^2 \times 0.30(1-0.30)}{0.03^2}$$

$$n = 896$$

Adjusting for the Finite Population Correction (FPC) factor we get final sample size $'n$:

$$'n = \frac{n}{1 + {}^{n}/_{N}} = \frac{896}{1 + {}^{896}/_{74}} = 69$$

The final sample size will be 69, the larger of the two, to cater for both hypothesis assumptions.

11. METHODOLOGY

The study was conducted between August 2013 and January 2014.

11.1 Method

Sequential patients (cases) above 12years presenting in the ENT H & N, Radio-oncology departments of KNH with histologically proven SCC of the hypopharynx were recruited to the study. Non- SCC histology were excluded from the study as well as those without histological diagnosis.

Initial explanation on the nature and scope as well as anticipated benefits of the study was done to all recruited subjects by the researcher. Informed consent was then obtained from the subjects or their guardians in case of minors and a study number assigned where-upon demographic data was entered in a proforma.

A medical history with primary focus on hypopharyngeal malignancy was obtained to include onset of symptoms, severity, duration and involvement of other regions.

History of smoking and alcohol intake was obtained to include age of onset of tobacco smoking, duration, type (filtered or non-filtered cigarettes, other forms of tobacco), number of sticks in pack years and whether they were still smoking cigarettes or not. History of family members who smoked, especially in the house, was also be obtained.

Alcohol intake was estimated by the number of days they consume alcohol, duration, amount and type of alcohol consumed. They were then classified as to whether they were heavy, moderate, social or not drinkers using the using the National Institute on Alcohol Abuse and Alcoholism (NIAAA) classification of drinking pattern[57].

Dietary history was also assessed with concentration on intake of green vegetables, fruits and carotenoids like carrots, tomatoes, to be able to determine the role of nutrition deficiency in

cancer development. The dietary history obtained was based on recall basis of how frequent the patient took certain food groups, and frequency of intake was grouped on daily, weekly, monthly intake, and those who rarely have intake of some food groups.

Prior history of anaemia, how it was diagnosed and mode of treatment was obtained to determine if it is a risk factor in some patients. Also in female patients parity was included due the risk of anaemia with increased parity.

History of Plummer – Vinson syndrome symptoms such as dysphagia, anaemia, with signs of glossitis and koilonychia were looked for in patients.

Patents occupational history was also obtained to establish exposure to asbestos, formaldehyde, metal.

Environmental exposure was enquired on regarding water source, type of fuel used, use of farming chemical.

Family history of cancer was also obtained to establish probable genetic role in development of disease in question.

Physical examination was done with emphasis on the ENT H & N regions. Information obtained was entered in a proforma.

11.2 Quality control

The proforma was pretested prior to the commencement of the study and appropriate changes made.

The principal investigator took the medical history and conduct the physical examination in all the patients to eliminate observer bias.

11.3 Data analysis

All data sheets were checked for completeness, consistency and accuracy. Data entry and cleaning was done in Microsoft Excel ®. A de-identification was done for all respondent identifiers which were deleted from the final analysis dataset. Descriptive analysis began with summaries of continuous variables; this data were presented descriptively in form of means (standard deviations [SD]) or medians (inter-quartile range [IQR]) as appropriate for the

continuous variables. Stata version12 (Stata Corp, College Station, Texas) was used for all the statistical analysis. Tables of counts (percentages) were created for the categorical variables and some pictorial presentation using bar graphs and pie charts as deemed appropriate.

11.4 Ethical considerations

(i) Study was done after approval by the Kenyatta National Hospital Ethical and Research Committee.

(ii) Participation in the study was voluntary, by consent of the patient or guardian and failure to give consent did not invite penalties.

(iii) No extra cost was incurred by the patient during the study.

(iv) Information obtained was kept confidential and raw data was kept secure by the researcher.

(v) Results of the study will be published and made available to members of the medical fraternity and the patients where relevant.

12.RESULTS

Patient Demographics and Characteristics

A total of 69 patients were recruited for the study from patient attendance register in the radiotherapy department and the admissions register in the ENT ward of KNH after meeting the inclusion criteria and after confirming diagnosis through their records. The mean age of the 69 patients in this evaluation was 50.6 years (SD = 15.2; Table 1), with the majority, 41(59.4%) being male (Figure 1). Majority of the patients presented in the 6^{th} and 7^{th} decade with 21(30.4%) and 16(23.1%) of patients respectively (Figure 2). Most of them either had primary or secondary level education, 36(52.2%) and 19(27.5%) respectively. The patients came from all the regions of the country but most came from Central, Eastern and Rift valley in that order (Table 2). Over half of the patients, 34 (52.3%), were involved in farming activities as their occupation. The female patients had a median parity of 5 (IQR = 2 – 7; Table 2).

Table 1 Patient Demographics

Demographic	n (%)
Male gender	41 (59.4)
Female	28 (40.6)

Age/Gender	Male (n)	Female (n)	Total (n) (%)
≤20years	1	3	4(5.8)
21 – 30 years	3	2	5(7.2)
31 – 40 years	6	5	11(15.9)
41 – 50 years	6	6	12(17.4)
51 – 60 years	12	9	21(30.4)
>60years	13	3	16(23.1)

Mean Age in years (SD) 50.6 (15.2)

Table 2 Patient characteristics

Patient characteristics	n (%)
Education	
None	2 (2.8)
Primary	36 (52.2)
Secondary	19 (27.5)
Tertiary	12 (17.4)
Region	
Eastern	21(30.4)
Central	24(34.7)
Nyanza	6(8.6)
Rift valley	7(10.1)
Western	3(4.3)
Northeastern	3(4.3)
Coast	2(2.8)
Nairobi	2(2.8)
Occupation*	
Farming	38(55.1)
Artisan	11(15.9)
Professional	6(8.6)
Other	20(28.9)
Unemployed	5(7.2)
Parity median (IQR)	5 (2 - 7)

*multiple-response (%s add to more than 100%)

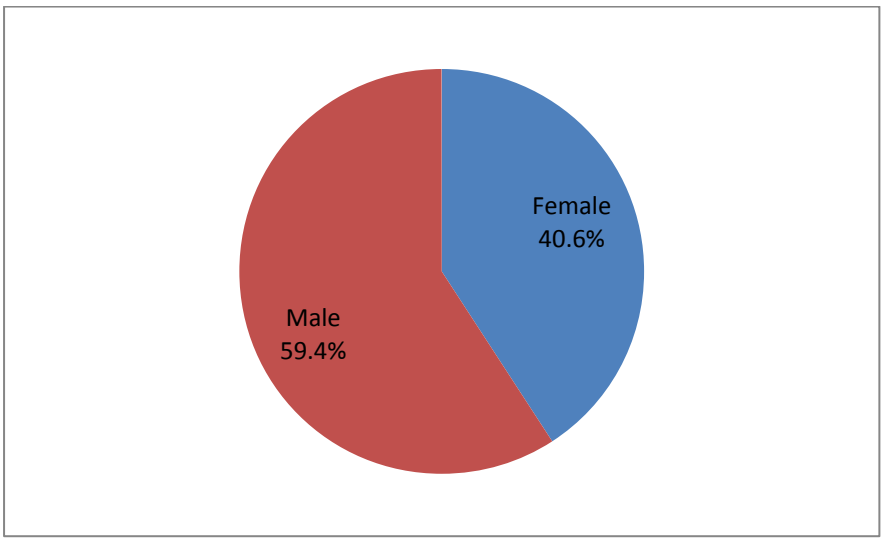

Figure 1 Gender of patients

Medical History

Only 3 (4.7%) had a family history of cancer. All of them, 69(100%), presented with dysphagia which had a median duration of 6 months (IQR = 6 - 9.5). Almost all, 65 (94.2%) presented with throat pain with a median duration of 4 months (IQR = 3 - 6). Most of the patients, 55(79.7%), had hoarseness of the voice for a median duration of 2 months (IQR = 2 – 3; Figure 2). Other commonly exhibited symptoms included difficulty in breathing and neck mass, 25 (36.2%) and 18(26.0%) respectively (Figure 3). The mean duration of difficulty in breathing was 1 month (IQR = 0.6 - 2) while the mean duration of neck mass was 2.5 months (SD = 1.2). None of them had Plummer-Vinson syndrome. A quarter of the patients had a history of use of farming chemicals for a median duration of 30 years (IQR = 15 - 30), with the duration of exposure recorded being from 2 – 40years.

Table 3 Medical History

Medical History	Duration (months) median (IQR)	n (%)
Family History of Cancer		3 (4.3)
Dysphagia	6 (4-9.5)	69 (100)
Throat pain	4 (3-6)	65 (94.2)
Hoarseness of Voice	2 (1-3)	55 (79.7)
Other symptoms *		
Cough	12	1 (1.4)
Difficulty in breathing	1.2 (0.6-2)	25 (36.2)
Foreign body sensation	12 (12-12)	1 (1.4)
Neck mass	2.5 (1.2)	18 (26.0)
Otalgia	1.1 (1-2)	3 (4.3)
Weight loss	4.5 (2-7)	4 (5.7)
Use of farming Chemicals		17 (24.6)
Farming Chemical duration (Years) Median (IQR)		30 (15 - 30)

*multiple-response (%s add to more than 100%)

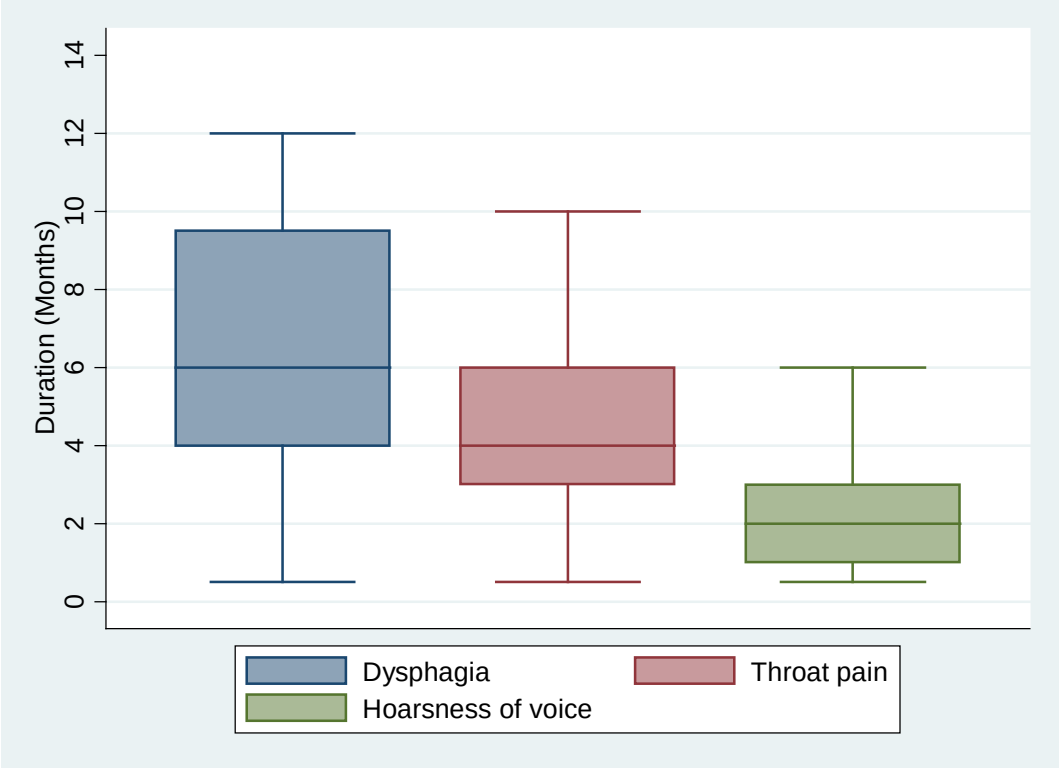

Figure 2 Duration of Dysphagia, Throat pain and Hoarseness of voice

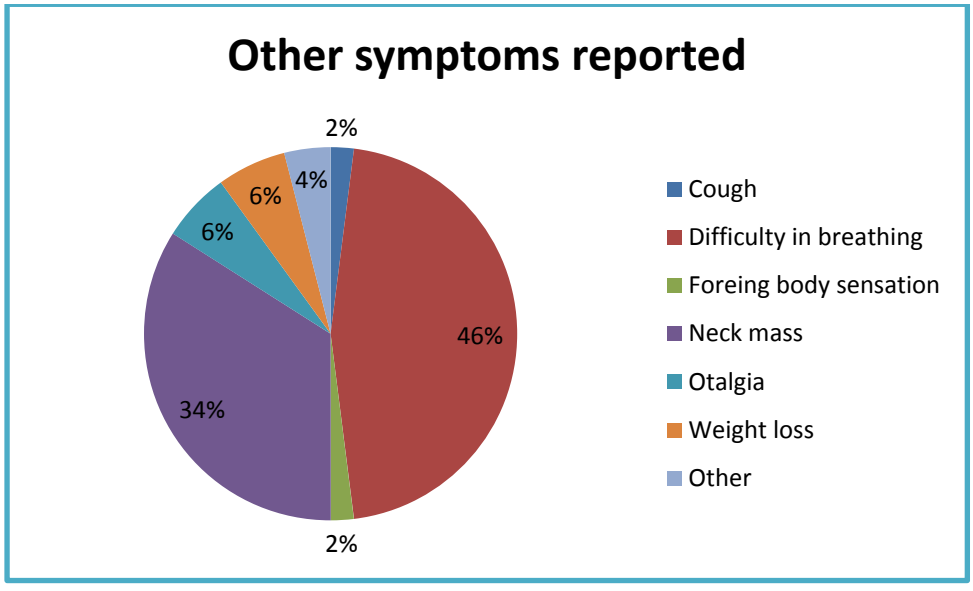

Figure 3 Other symptoms reported by patients

Water source

The main water sources used by the patients were river, rain water and piped water; 46(66.6%), 21(30.4%) and 18(26.0%) respectively (Table 4).

Table 4 Water Source

Water source*	n (%)
Borehole	13 (18.8)
Piped	18 (26.0)
Rain water	21 (30.4)
River	46 (66.6)
Well	8 (11.5)

*multiple-response (%s add to more than 100%)

Smoking History

About half, 36 (52.1%), of the patients were smokers (Figure 4). Most of the males, 36(87.8%), were smokers while none of the females smoked. The mean duration of smoking was 29 years (SD = 10.7). The most widely smoked cigarette type was filtered 32(97%) and hand rolled 8(24.2%). The median pack years per patient was 23.8 years (IQR = 15 – 40; Table 5 and figure 5). The median duration since stopping to smoke was 1 year (IQR = 0.6 - 3). Just under a quarter, 15(23.85), of the patients had secondary smoking for a median duration of 18 years (IQR = 5 - 26).

Table 5 Smoking History

Smoking History	n (%)
Smokers	36 (52.2)
Male Smokers	36 (87.8%)
Female Smokers	0 (0%)
Smoking Duration (Years) Mean (SD)	29 (10.7)
Cigarette Type *	
Filtered	35 (97)
Non-filtered	2 (5.5)
Hand rolled	9 (25)
tobacco	1 (2.7)

Pack years for patient (years)	
0 – 10	6 (16.7)
11 – 20	8 (22.2)
21 – 30	10 (27.8)
31 – 40	5 (13.9)
>40	8 (22.2)
Pack years per patient Median (IQR)	22.5 (15 - 40)
Duration since stopping to smoke (years) Median (IQR)	1 (0.5 - 3)
Secondary smoking	15 (23.8)
Secondary smoking (years) Median (IQR)	18 (5 - 26)

*multiple-response (%s add to more than 100%)

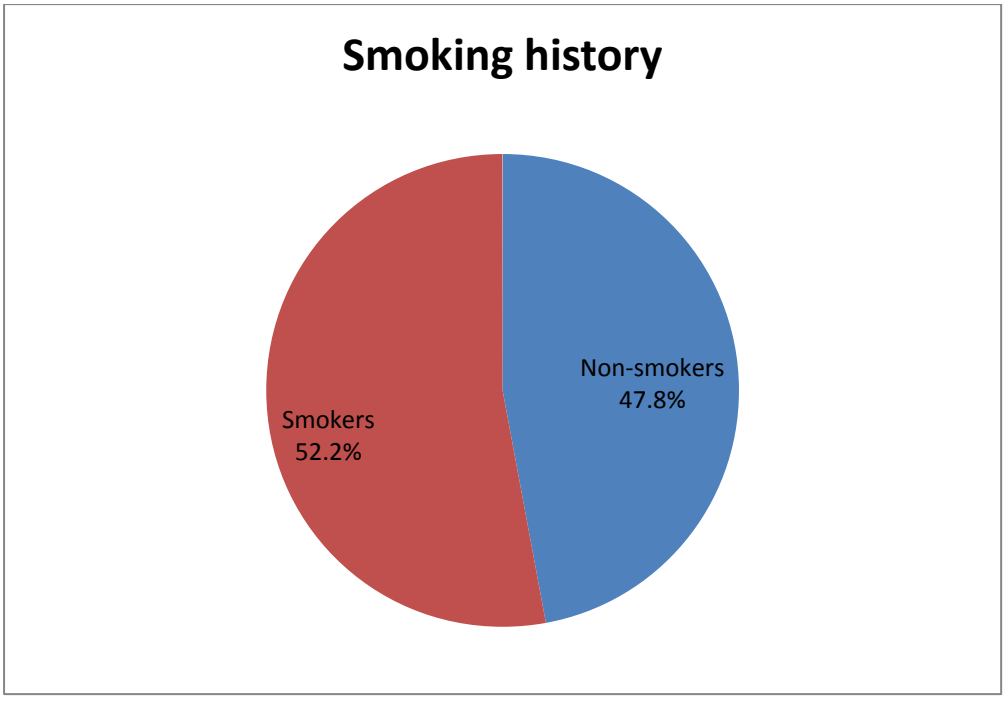

Figure 4 Overall smoking Status

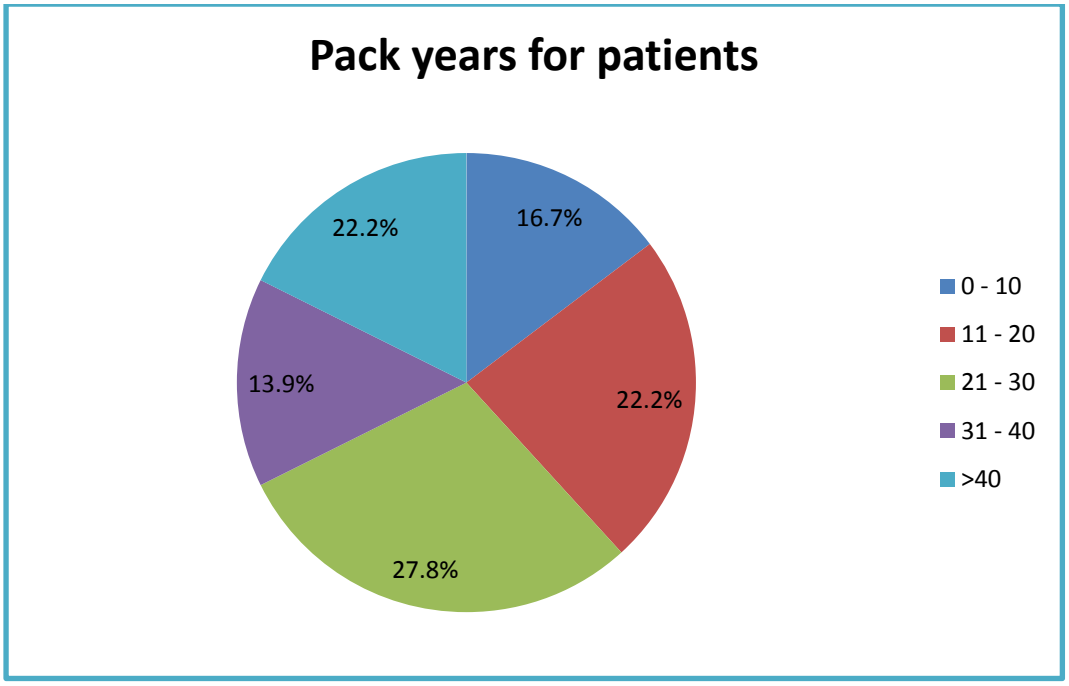

Figure 5 Pack years for patients who smoked

Fuel and Ventilation

Majority of the patients used firewood and charcoal, 64 (93.8%) and 50(70.3%) respectively (Table 6). Most of the houses, 62(89.9%), had a window and door ventilation.

Table 6 Fuel and Ventilation

Fuel and House Ventilation	n (%)
Fuel *	
Firewood	64 (92.7)
Paraffin	14 (20.3)
Charcoal	50 (72.5)
Gas	4 (5.8)
Other	1 (1.4)
Ventilation in House	
Door	7 (10.1)
Window & Door	62 (89.9)

*multiple-response (%s add to more than 100%)

Alcohol Consumption

Half the patients, 35(50.7%), took alcohol (Figure 6). Among those who took alcohol most also smoked 32 (91.4%). The mean age of starting to drink was 19.9 years (SD= 4.7). Most of those who took alcohol drank daily, 21(60%). The alcohol quantities varied among the patients with about quarter of the patients, 16(45.7%), being very heavy drinkers (Figure 7). Only 4 patients reported the use of miraa (khat). The median duration since stopping to smoke was 2.5 years (IQR = 0.5 – 10; table 7).

Table 7 Alcohol Intake

Alcohol History	n (%)
Alcohol intake	35 (50.7)
Alcohol intake & Smoke	32 (91.4)
Age of starting to drink (years) Mean (SD)	19.9 (4.7)
Types of alcoholic drinks*	
Traditional	23 (65.2)
Beer	27 (77.1)
Spirits	15(42.8)
Wine	0
Other**	1 (1.8)
Number of days drink in a week	
Once	2 (5.7)
Twice	4 (11.4)
Three times	4 (11.4)
Four times	3 (8.6)
Daily	21 (60)
Alcohol intake pattern	
Light drinkers	3 (8.6)
Moderate drinkers	7 (20)
Heavy drinkers	9 (25.7)
Very heavy drinkers	16 (45.7)
Duration since stopping to drink (years) Median (IQR)	2.5 (0.5 - 10)

* multiple responses (%add to more than 100%). ** Elicit brews e.g. “changaa”

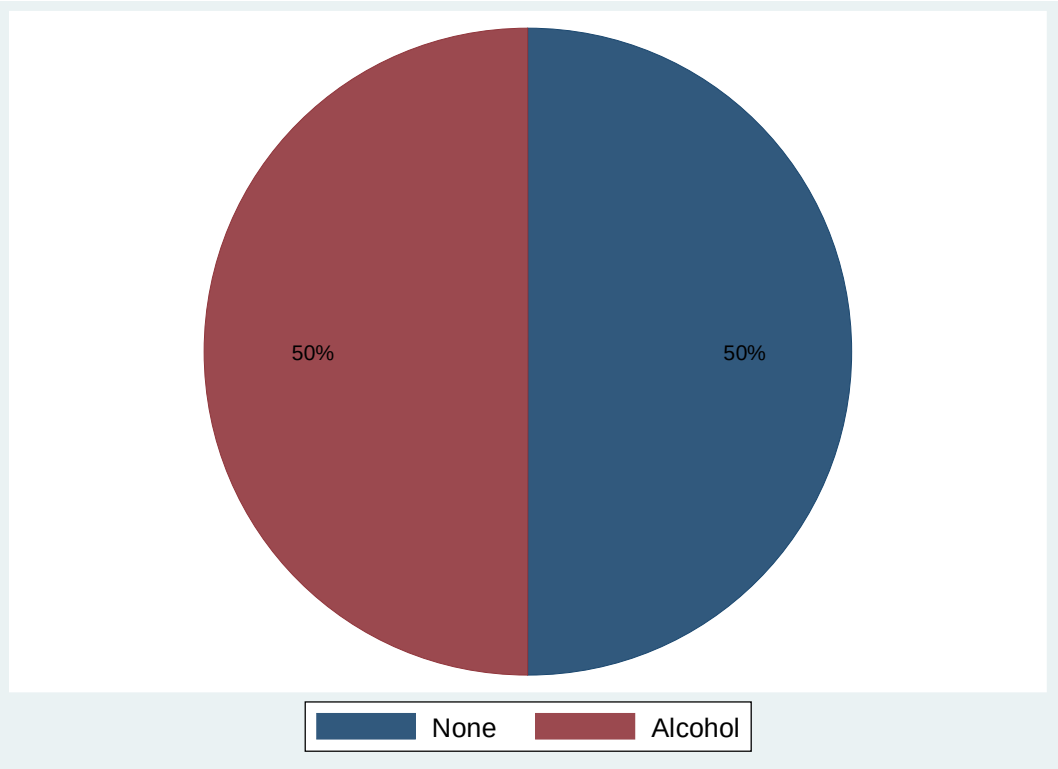

Figure 6 Alcohol status

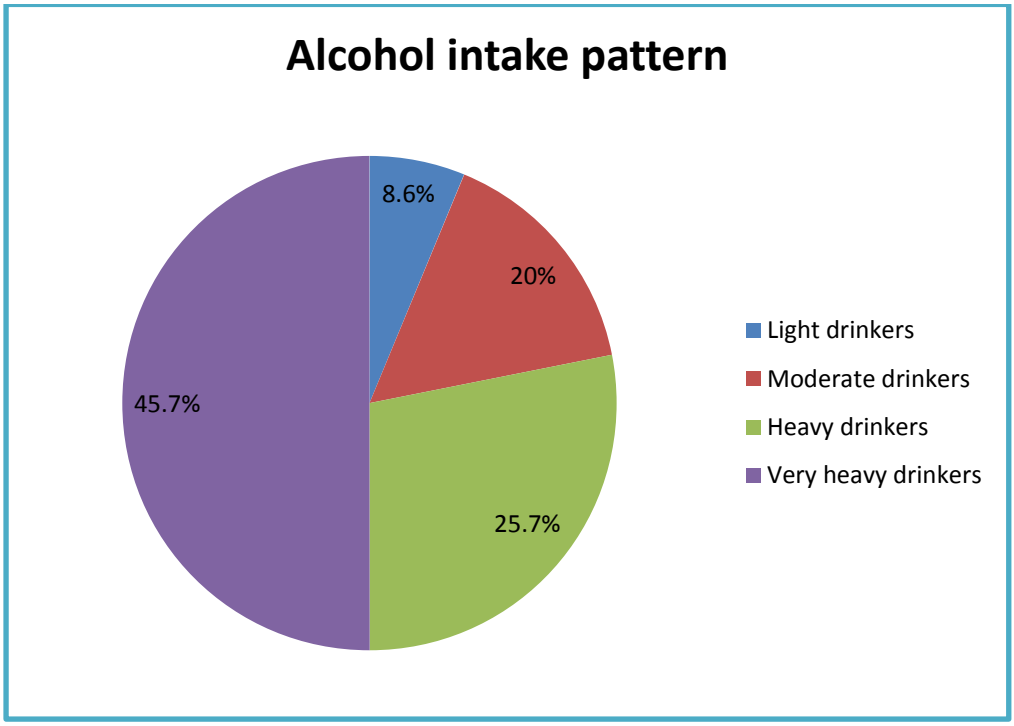

Figure 7 alcohol intake pattern for patients

Nutrition

Less than half of the patients 25(37.9%), ate green vegetables daily. Equally few, 18(26.1%), ate fruits every day. However over half, 43(62.3%) of the patients had a daily intake of carotene. Majority of the patients, 54(78.2%), took maize at least once a week (Table 8).

Table 8 Nutrition History of patients

Nutritional History	n (%)
Green Vegetables	
Everyday	25 (37.9)
Once a week	34 (49.3)
Once a month	10 (15.1)
Fruits	
Everyday	18 (26.1)
Once a week	38 (55.0)
Once a month	13 (18.8)
Carotene	
Everyday	43 (62.3)
Once a week	24 (34.8)
Once a month	2 (2.9)
Maize	
Everyday	11 (15.9)
Once a week	54 (78.2)
Once a month	4 (5.8)

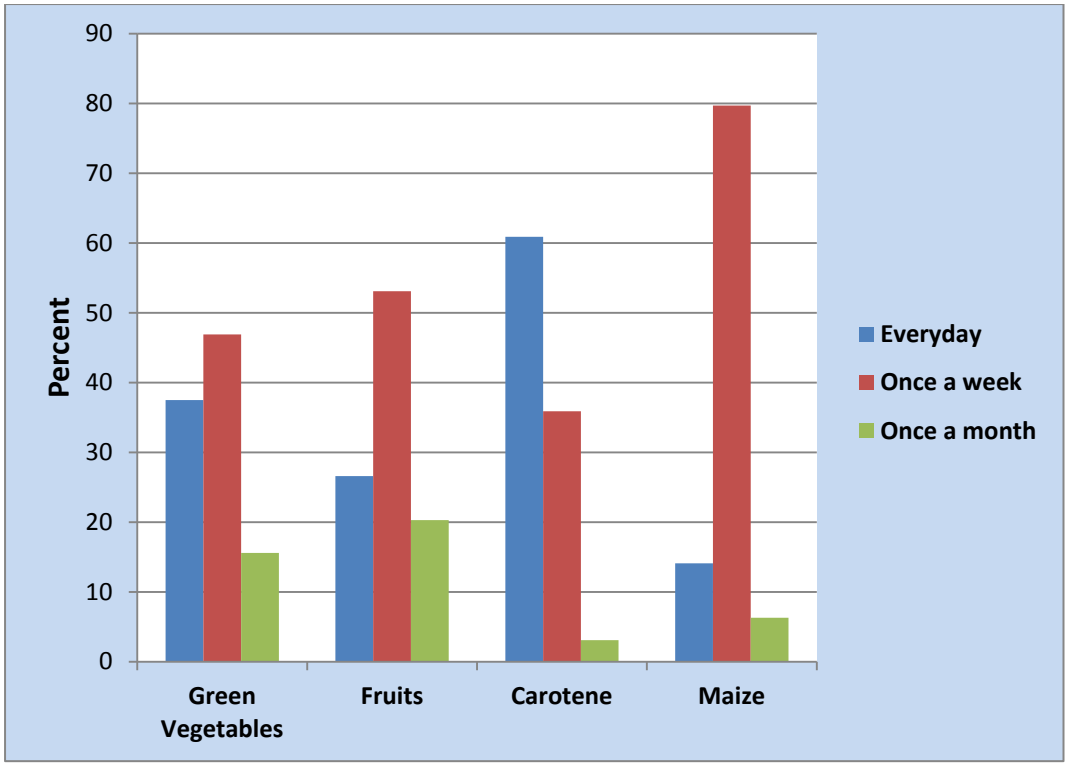

Figure 8 Nutrition intake of patients for vegetables, fruits, carotene and maize

Histology

The commonest histological type of tumour was moderately differentiated SSC and well differentiated SSC, 33 (47.8%) and 28 (40.5%) respectively. The most common tumour stages were T4 and T3 which were found in 40 (57.9%) and 16 (23.1%) of the patients respectively. The most common sub site involved was Pyriform fossa 33(47.8%) while 23 (33.3%) were indeterminate (Table 9).

Table 9 Histology, Tumour Stage and Sub site

Histology, Stage and Sub-Site	n (%)
Histology	
Well differentiated SSC	28 (40.5)
Moderately differentiated SSC	33 (47.8)
Poorly differentiated SSC	7 (10.1)
Undifferentiated	1 (1.4)
Tumour Stage	
T1	1 (1.4)

T2	11 (15.9)
T3	17 (24.6)
T4	40 (57.9)
Sub site *	
Postcricoid	16 (23.1)
Pyriform fossa	33 (47.8)
Posterior wall	6 (8,7)
All	7 (10.1)
Indeterminate	23 (33.3)

*multiple-response (%s add to more than 100%)

13.DISCUSSION

Demographics, Tumour Stage and Histology

Hypopharyngeal carcinoma is considered as a silent disease by some authors due to the fact that patients will present at an advanced stage of the illness. Majority of patients present in their 7th decade though younger patients are also being affected. In the current study while the mean age was 50.6 years majority of patients presented in the 6th and 7th decade at 30.4% and 23.1% respectively. There were a number of patients below 40 years of age (28.9%). This is comparable to a study by Wahid et al[47] who found a mean age of 57.26 years (SD 0f 14.01) with majority presenting in the 6th and 7th decade followed by 4th and 5th decades. In one study in Austria by Swoboda H et al it was noted that there was an increase in the incidence of hypopharyngeal carcinoma among the younger age groups compared to the older age group in which there was a decline[58].

Genetic predisposition to cancer was only captured in 4.7% of the patients in this study with a family history of cancer ranging from larynx, colon and lung cancer. Studies have shown that increased risk of cancer is present in first degree relatives of patients with head and neck cancer though it is generally agreed that genetics do not act alone but rather within a multiplicity of factors[59].

The commonest histology was moderately differentiated SCC in 46.9% with a majority of the patients having late presentation at T4 in 57.9%. This has also been seen in India where 39% of patients were in stage III and 23% were in Stage IV disease at time of presentation as it is generally noted that in HNC patients mostly present in late stages and hypopharyngeal carcinoma is not an exception[60]. Onyango et al[56] also demonstrated that there was a pattern of late presentation of patient with HNC at the KNH. The commonest subsite was the pyriform in 47.8% of the patients which was comparable to the study by Wahid et al[48] where 44% of patients had tumour in the pyriform fossa, other authors have also reported the same[61,62].

Presenting Features

Dysphagia was seen in 100% of the patients, similar to findings by Wahid et al[48] where 92%, Mendenhall et al[11] 46%, Hall et al[63] 53% who reported as the commonest symptom. Hoarseness of voice was reported in 82.8% and this change in voice is considered to be a late

symptom and will be due either invasion of the larynx or involvement of the recurrent laryngeal nerve or cricoarytenoid joint fixation.

Plummer-Vinson syndrome was not reported in any of the patients in this study probably due to lack of awareness of the symptoms. Though Wynder at al[64] found a relation between Plummer-Vinson syndrome and hypopharyngeal cancer in Sweden, Larsson et al[35] later reported a reduced incidence of the syndrome due to improved healthcare and improved nutrition. In the Kenya Demographics and Health Survey (KDHS) 2008-2009 the total fertility rate (TFR) for Kenya was 4.9 children per woman[65]. High parity was observed in 53.6% of the female patients with 5 or more children though no history of anemia was reported to see if there was a predisposition to developing the cancer. In KDHS 2008-2009 69% of mothers who attend antenatal care received iron supplementation[65]. In Europe iron supplementation has been included in antenatal programs to prevent anemia in women at risk of deficiency or those already having deficiency from the onset up to the postpartum period[66].

Occupation, Environmental Exposures

In the current study majority of patients were from rural parts of the country referred to KNH for treatment with the three leading counties being Muranga, Meru and Kiambu with 15.63%, 9.38% and 6.25% of the patients respectively. Farming was a common occupation in those patients who came from these rural regions where there was notable use of farming chemicals with 25% of patient being exposed for a median of 20years (IQR 15-30). A study done in India by Mishra et al[60] had 38% male and 17% female who were housewives exposed to pesticides and fertilizer presenting with head and neck cancer mostly oral, oropharyngeal and laryngeal cancers. Uzcudum et al in a study in Spain showed that environmental exposure to pesticides was a risk to oropharyngeal and hypopharyngeal cancer[67]. Pesticides have been implicated in cancer of the breast, HN lymphoma, lung and prostate cancer with an increased risk with increased duration of exposure[68].

The main water source was from the river in 66.6% of the patients which exposed the patients to untreated water that could possibly be contaminated from runoff chemicals from farms. Most of the patients in this study also had more than one water source. Other common sources were harvested rain water & borehole in that order. According to KDHS 2008-2009 45.8% of rural population had non-improved water sources i.e. unprotected dug wells & streams, surface water from lakes. Since this was a descriptive study, it was not possible to

test the water sources for possible pollutants that could possibly be a cause of hypopharyngeal cancer. In Marsabit, located in Northern Kenya, water analysis done found toxic chemicals like arsenic, nitrates and nitrites in the water which was linked to cancer of the oesophagus reported in the region[69].

The main source of fuel for cooking was firewood followed by charcoal with 92.7% and 72.5% respectively. The indoor air pollution from charcoal burning is a known carcinogen while that of biomass (wood) is a probable carcinogen[70,71]. The main carcinogens are benzo(a)pyrene, formaldehyde and benzene from air pollutants from use of charcoal and firewood. Majority of population in the Kenya rural setting rely on natural sources of fuel creating a public health concern due to the fact that poor ventilation is also noted in households especially the cooking area as seen in this study. In China Pan G et al[72] and in India Sapkota A et al[73] showed in their studies that indoor air pollution by charcoal burning was a risk for oesophageal and hypopharyngeal cancer. In the current study there were 89.9% of patient reported presence of both a door and window in the home but admitted the size was small. This may suggest that long term exposure to indoor air pollution from use of firewood and charcoal may be a risk for hypopharyngeal cancer.

Smoking, Alcohol and Nutrition

Smoking was a significant characteristic with over half (52.1%) of the patients being smokers. All of the smokers were male. Patients who had a history of passive smoking were 10.7%. Majority of those with history of smoking had between 21-30 pack years while 18.18% had over 40 pack years. Some patients reported not having stopped to smoke since onset of illness and diagnosis. Mishra found that among HNC patients in India smoking habit was initiated by 2nd and 3rd decade in 73% and 18% respectively, while 66% smoked for more than 20years with 10-20 cigarettes smoked per day.[60] In a study by Kushihashi et al[74] there was found to be increased risk of cancer with increased duration and quantity of smoking and especially for oral cavity, larynx and hypopharyngeal. Parson[75] did a review of literature of smoking on respiratory malignancies and found that there was a positive relation between cessation of smoking and reduction of risk with improved treatment outcome in lung cancer.

Alcohol consumption was also noted in half of the patients with an early mean age of onset of drinking of 19.9years. Heavy and very heavy drinkers were the majority and this showed that

most of the patients had prolonged exposure to alcohol. Mishra also found that early onset of drinking in 2nd and 3rd decade was present in India among HNC patients with 26% of patients having history of alcohol intake and a total duration of intake of 10-20years.[60] Early onset of drinking alcohol with prolonged duration combined with high frequency of intake was found to be a high risk for developing HNC with an OR2.04, 95% CI in a study by Hashube et al[76]. A dose effect was also observed by Menvielle et al[22] for both alcohol and smoking and if both factors were present the effect was multiplicative and in the current study 91.4% of those with history of alcohol intake had history of concurrent smoking for similar duration.

Both fruits and vegetable were consumed once a week by half of the patients which is poor compared to the recommended daily intake. Low fruit and vegetable intake coupled with consumption of alcohol and smoking has been found to increase cancer development [77,78]. It is known that daily intake of fruits and vegetable has a protective effect on development of HNC through provision of Vitamin A, Vitamin C and folate. Various studies have been done demonstrating a protective effect of fruits and vegetables to HNC and daily intake was found to reduce the overall risk of cancer by 50% [79].

Study Limitations

There were a couple of limitations to this study one being that the information obtained through a questionnaire was through recall which could have been associated with recall bias. This is a hospital based study so the population sampled was only those who made it to hospital and proximity may be a factor to why some regions recorded low number of patients. The other limitations was that a number of patients took traditional brews and these were difficult to quantify for some due to the fact that no packaging is done for them and for majority of them the alcohol content is unknown as it is not standardized.

14.CONCLUSION AND RECOMMENDATIONS

From the current study it appears that smoking and chronic alcohol consumption most likely contributed to development of hypopharyngeal carcinoma. Majority of patients also came largely from the rural regions of the country with significant exposure to farming chemicals for long durations. Use of biomass fuel for cooking was common which may cause indoor air pollution as well as water from the river which could expose population to run-off chemicals. In view of the above presented characteristics there is need for further studies to determine the causal relationship between development of hypopharyngeal carcinoma and these factors. Also an epidemiologic study of the different regions needs to be done to determine the prevalence of the disease and the associated risk factors per region.

15. APPENDIX I

GENERAL PATIENT INFORMATION AND CONSENT FORM

Introduction

Participation in this study is voluntary. We aim to find out the common risk factors for patients with hypopharyngeal carcinoma in order to come up with better management guidelines including prevention measures.

What is hypopharyngeal carcinoma?

It is cancer of the throat involving parts that have to do with swallowing.

What is involved in this study?

Once you consent to participate, we will take a medical history and carry out an ENT examination. A questionnaire with be used to fill in information to do with history of smoking, alcohol consumption, occupation as well as diet history.

Are there any risks involved?

There are no risks involved.

Will I be penalized for not participating?

No, you will receive the same attention and treatment as those who choose to participate.

What benefits will I get if I participate?

The benefits of the study will be towards creating more awareness in the public and for those with suspected cancer to have early diagnosis and treatment.

What about confidentiality?

All the information we obtain from you will be kept confidential.

How much will it cost me?

No extra cost will be incurred.

What are my rights as a participant?

Participation in the study is voluntary. Once inducted in the study, you can choose to discontinue at any time. This will not cause discrimination.

What do you do with the information you get?

This information will help us find out more about what are the risk factors for developing hypopharyngeal carcinoma.

Are you satisfied with the information given?

If yes and you are willing to participate or let child participate, please fill in and sign the consent below.

KISWAHILI
MAELEZEO YA UTAFITI NA KIBALI

Mwanzo
Kushiriki kwa utafiti huu ni kwa hiari yako. Tunalenga kufanya utafiti juu ya madhara yanayo sababisha kuenea kwa ugonjwa wa saratani ya koo.

Je, saratani ya koo ni ipi?
Hii ni mojawapo ya saratani inayo athiri sehemu ya koo inayo wezesha mtu kumeza.

Utafiti huu unahusu nini?
Ukisha patiana kibali, historia yako ya ugonjwa itachukuliwa alafu na kuchunguzwa. Alafu utajaza karatasi iliyo na maswali kuhusu unywaji wa pombe, uvutaji sigara, aina ya chakula unazo kula, kazi unayoshiriki na mengineo ili kuona ni yapi yaliyochangia.

Niko hatarini kushiriki?
Hapana humo hatarini.

Je, nita adhibiwa kwa kukosa kushiriki?
Hapana, hautabaguliwa kwa matibabu na yataendelea kama ilivyo pangwa.

Nitaridhishwa aje na utafiti huu?
Utafiti huu utasaidia wauguzi kwa kuwapa mawaitha wagonjwa na wananchi kwa jumla yale yanayochangia kupata saratani hii, na illi iwe inagunduliwa mapema kwa walio adhiriwa ili kupokea matibabu mapema.

Na kuhusu recordi zangu kuwekwa siri?
Rakodi zako za ugonjwa hazitatolewa hadharani kwa yeyoye.

Itanigharimu pesa ngapi?
Hautahitaji kutumia pesa zozote za ziada.

Na je nikitaka kujiondoa?
Ukitaka kujiondoa waweza kufanya wakati wowote. Tendo hilo halita fanya ubaguliwe kwa aina yeyoye.

Umereithika na maelezo umepata?
Kama umerithika na unataka kusiriki katika utafiti huu, piga sahihi kwa form iliyo hapo chini.

ASSENT FORM FOR MINORS

My name is Dr. Muturi, Caroline Kirigo. I am trying to find out what are the causes of the disease you have in your throat, because I want to let more people aware of the causes and prevent more people from becoming sick. If you would like, you can be in my study.

If you decide you want to be in my study, you will answer some questions on your history of illness, I will examine you concentrating on the ear, nose & throat area, and the information will be filled in a form that I have prepared.

There will be no risks involved in taking part in this study.

Other people will not know if you are in my study. I will put things I learn about you together with things I learn about other patients your age, so no one can tell what things came from you. When I tell other people about my research, I will not use your name, so no one can tell who I am talking about.

Your parents or guardian have to say it's OK for you to be in the study. After they decide, you get to choose if you want to do it too. If you don't want to be in the study, no one will be mad at you. If you want to be in the study now and change your mind later, that's OK. You can stop at any time.

My telephone number is 0733244768. You can call me if you have questions about the study or if you decide you don't want to be in the study any more.

I will give you a copy of this form in case you want to ask questions later.

Agreement

I have decided to be in the study even though I know that I don't have to do it. Dr. Muturi, Caroline Kirigo has answered all my questions.

_____ _____

Signature of Study Participant Date

_____ _____

Signature of Researcher Date

16.APPENDIX II

CONSENT FOR THE STUDY

The participation of your child/self in this study is entirely voluntary.

I…….. ID No…….. Of.....

study no…… do hereby consent for my child/myself to be included in this study on risk factors of hypopharyngeal Carcinoma. The nature of the study has been fully explained to me by Dr…… I have not been promised any material gain to participate.

Signed……. (Patient/guardian)

Date…….

KIBALI CHA UTAFITI

Kushiriki kwako/mtoto wako katika utafiti huu ni kwa hiari yako.

Mimi …….. Id No…… Anwani…….

wa……nambari ya utafiti……. Nimekubali mimi/mtoto wangu kuhusishwa katika utafiti huu unaongalia maradhi yanayojitokeza katika sehemu za sikio, pua, koo, kichwa na shingo kutokana na saratani ya sehemu ya koo. Nimefahamu baada ya kusoma na kufahamishwa na

Dr…….Hakuna malipo nitapewa.

Sahihi…… (Mzazi/Mgonjwa)

Tarehe……

CONTACTS

Researcher	:	Dr Muturi Caroline Kirigo P.O. Box 66328-00800 Email: carolinekirigo@yahoo.com Mobile: 0733244768
Secretary KNH/UoN Ethics committee	:	Tel: 020 2726300-9

17.APPENDIX III

QUESTIONNAIRE

IP NO: _____ STUDY NO: _____

AGE: _____ YRS SEX: _____

REGION / COUNTY_____

PARITY_____

IS THERE FAMILY HISTORY OF CANCER_____

SYMPTOM	YES	NO	DURATION
DYSPHAGIA	☐	☐	_____
THROAT PAIN	☐	☐	_____
HOARNESS OF VOICE	☐	☐	_____
OTHERS	☐	☐	_____

SYMPTOMS AND SIGNS OF PLUMMER-VINSON SYNDROME

	YES	NO
DYSPHAGIA	☐	☐
GLOSSITIS	☐	☐
KOILONYCHIA	☐	☐
OESOPHAGEAL WEBS	☐	☐

OCCUPATION _____

ENVIROMENTAL EXPOSURE	YES	NO
FARMING CHEMICALS	☐	☐
ASBESTOS	☐	☐

FORMALDEHYDE ☐ ☐

COAL DUST ☐ ☐

IF YES FREQUENCY_____ DURATION _____

WHERE DOU YOU GET YOUR WATER SOURCE _____

EDUCATION LEVEL

Primary ☐ Secondary ☐ Tertiary ☐

HAVE YOU EVER SMOKED ☐ YES ☐ NO

DURATION OF SMOKING ☐ YRS

TYPE OF CIGARETTE Filtered ☐ Non-filtered ☐

Hand rolled ☐ tobacco ☐

QUANTTITY OF CIGARETTES SMOKED ☐ PER DAY

WHEN DID YOU STOP SMOKING ☐

HOW LONG SINCE YOU STOPPED SMOKING ☐ YEARS/MONTHS

DO YOU LIVE WITH A SMOKER ☐ YES ☐ NO

DURATION ☐ YRS

DOES HE/SHE SMOKE INSIDE THE HOUSE ☐ YES ☐ NO

DOES THE HOUSE HAVE A LIVING ROOM AND A KITCHEN _____

TYPE OF VENTILATION IN HOUSE

	YES	NO
Windows	☐	☐
Doors	☐	☐
Both	☐	☐

TYPE OF FUEL USED FOR COOKING

	YES	NO
FIRE WOOD	☐	☐

PARAFFIN ☐ ☐

CHARCOAL ☐ ☐

GAS ☐ ☐

COWDUNG ☐ ☐

OTHER ☐ ☐

HAVE YOU EVER CONSUMED ALCOHOL ☐ YES ☐ NO

DURATION ☐ YRS

KIND OF ALCOHOLIC DRINK

Traditional ☐ Beer ☐ Spirits ☐ Wine ☐ Other ☐

AGE YOU STARTED DRINKING ☐ YRS

HOW MANY TIMES A WEEK _____

HOW MUCH DO YOU DRINK ☐ PER DAY

IF STOPPED DRINKING HOW LONG AGO _____

DIETARY HISTORY	everyday	once a week	once a month	hardly ever
GREEN VEGETABLES	☐	☐	☐	☐
FRESH FRUITS	☐	☐	☐	☐
β CAROTEN (carrots,, tomatoes, spinach)	☐	☐	☐	☐
MAIZE	☐	☐	☐	☐

TUMOUR

HISTOLOGY G1-Well differentiated ☐

G2- Moderately differentiated ☐

G3- Poorly differentiated ☐

G4- Undifferentiated ☐

STAGE

T1 ☐

T2 ☐

T3 ☐

T4 ☐

SUBSITE

Postcricoid region ☐

Pyriform fossa ☐

Posterior pharyngeal wall ☐

All ☐

Indeterminate ☐

18. APPENDIX IV

AJCC 2010 Staging[10].

Table 1. Primary Tumour (T) [(a)]

TX	Primary tumour cannot be assessed.
T0	No evidence of primary tumour.
Tis	Carcinoma *in situ*.
	Hypopharynx
T1	Tumour limited to 1 subside of hypopharynx and/or ≤2 cm in greatest dimension.
T2	Tumour invades >1 sub site of hypopharynx or an adjacent site, or measures >2 cm but not >4 cm in greatest dimension without fixation of hemilarynx.
T3	Tumour >4 cm in greatest dimension or with fixation of hemilarynx or extension to oesophagus.
T4a	Moderately advanced local disease.
	Tumour invades thyroid/cricoids cartilage, hyoid bone, thyroid gland, or central compartment soft tissue's
T4b	Very advanced local disease.
	Tumour invades prevertebral fascia, encases carotid artery, or involves mediastinal structures.

[a]Hypopharyngeal Cancer Treatment (PDQ). National Cancer Institute[10]. www.cancer.gov/pdq/treatment/hypopharyngeal

Table 2. Regional Lymph Nodes (N)[a,b]

NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension.
N2	Metastases in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension.
N2a	Metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension.
N2b	Metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension.

N2c	Metastases in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension.
N3	Metastasis in a lymph node >6 cm in greatest dimension.

[a]Hypopharyngeal Cancer Treatment (PDQ). National Cancer Institute. www.cancer.gov/pdq/treatment/hypopharyngeal

[b]Metastases at level VII are considered regional lymph node metastases.

Table 3. Distant Metastasis (M)[a]

M0	No distant metastasis.
M1	Distant metastasis.

19.APPENDIX V

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)

REFERENCES

1. Otoh EC, Johnson NW, Danfillo IS, Adeleke AO, Olasoji HA. Primary head and neck cancer in North Eastern Nigeria. West African Journal of Medicine. 2004;23:305-313.
2. Fan CY. Epigenetic alterations in head and neck cancer: prevalence, clinical significance, and implications. Curr Oncol Rep.2004;6(2):152-161.
3. Onakayo PA, Nwaorgu OG, Adenipekun AO, Aluko AA, Ibekwe TS. Quality of life in patients with head and neck cancers. Journal National Medical Association 2006;98(5):765-770.
4. Goldenberg D, Lee J, Koch WM, et al. Habitual risk factor for head and neck cancer. Otolaryngology Head and Neck Surgery. 2004;131(6):986-993.
5. Mutuma GZ, Rugut-Korir A. Nairobi Cancer registry. Kenya Medical Research Institute. Cancer Incidence Report 2000 – 2002.
6. Chang MF, Wang H-M, Kang C-J, et al. Treatment result for hypopharyngeal cancer by different strategies and Its secondary primary – an experience in Taiwan. Radiation Oncology. 2010;5:91.
7. Sobin LH, Witterkind CH. TNM classification of malignant tumors, 5th edition. John Wiley and Sons, Inc. New York.1997;25-32.
8. Watkinson JC, Gaze MN, Wilson JA. Stell and Maran's Head and neck Surgery: Tumours of the Hypopharyngeal. 4th Edition.2000. Page 335-356. Reed Education and Professional Publishing Limited.
9. National Cancer Institute. Hypopharyngeal Cancer Treatments (PDQ). Available on www.cancer.gov/pdq/treatment/hypopharyngeal.
10. Barnes L, Johnson JT. Pathologic and clinical considerations in the evaluation of major head and neck specimens resected for cancer. Part I. Pathol Ann 1986;21(1):173-250.
11. Mendenhall WM, Werning JW, Pfister DG: Treatment of head and neck cancer. In: DeVita VT Jr, Lawrence TS, Rosenberg SA: Cancer: Principles and Practice of Oncology. 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins, 2011, pp 729-780.
12. Tuyns AJ, Esteve J, Raymond L, et al. Cancer of the larynx/hypopharynx, tobacco and alcohol: IARC international case-control study in Turin and Varese (Italy),

Zaragoza and Navarra (Spain), Geneva (Switzerland) and Calvados (France). Int J Cancer 1988; 41:483-491.

13. Uzcudun AE, Bravo Fernández P, Sánchez JJ, et al.: Clinical features of pharyngeal cancer: a retrospective study of 258 consecutive patients. J Laryngol Otol. 2001;115(2):112-8.
14. Tobacco smoke and Involuntary smoking. Lyon France. International Agency of Research on Cancer. IARC monographs on the Evaluation of carcinogenic risk to humans. 2004;Vol 83.
15. Mossman BT, Eastman A. Carcinogenesis in the respiratory tract. In: MacDowell EM. Lung carcinomas. Churchill Livingstone 1987; 129-161.
16. Bresnick E, Eastman A. Alkylation of mammalian cell DNA,persistence of adducts and relation to carcinogenesis. Drug Metabolism Review. 1982;13(2):189-205.
17. Bresnick E Nuclear aryl hydrocarbon hydroxylase and interaction of polycyclic aromatic hydrocarbons with nuclear components. Archives of Biochemistry and Biophysics 1977; 181:257-269.
18. Hoffman D, Hecht SS. Nicotine derived N-nitrosamines and tobacco related cancer: current and future direction. Cancer Research 1985;45:935-944.
19. Cayama E, Tsuda H, Sarma D, Farber E. Initiation of chemical carcinogenesis requires cell proliferation. Nature 1978;275:60-62.
20. Zheng Z. Tobacco carcinogen detoxifying enzyme UGT1A7 and its association with oropharyngeal cancer risk. J Natl Cancer Inst 2001;93:1411-1418.
21. Helmut KS, Stickel F. Molecular mechanisms of alcohol-induced carcinogenesis. Nature Review Cancer 2007;7:599-612.
22. Menvielle G, Luce D, Goldberg P, Bogel L, Lecler A. Smoking, alcohol drinking and cancer risk for various sites of the larynx and hypopharynx; A case-control study. Eur J Cancer Prev 2004;13(3):165-172.
23. Zeka A, Gore R, KreibelD. Effects of alcohol and tobacco on aerodigestive cancer risk; a meta-regression analysis. Cancer Causes Control.2003;14(9):897-906.
24. Poschi G, Stckel F, Wang XD, Seitz HK. Alcohol and cancer: genetic and nutritional aspects. Proceedings of Nutritional Society 2004;63:65-71.

25. Espina N, Lima V, Leiber CS, Garro AJ. In vitro and In vivo inhibitory effect of ethanol and acetaldehyde on O^6-methylguanine transferase. Carcinogenesis 1988;9:761-766.
26. Yokoyama A, Maramatsu T, Ohmon T. Alcohol related cancers and aldehyde dehydrogenase in Japanese alcoholics. Carcinogenesis 1998;19:1383-1387.
27. Maier LT, Sennewald E, Heller GF, Waidauer LT. chronic alcohol consumption, the key risk factor for pharyngeal cancer. Otolaryngol Head and Neck Surge 1994;110:168-173.
28. Grabb DW, Pinaris J, Hasanadka R, et al. Alcohol and retinoids. Alcohol, Clinical and Experimental Research 2001:2075-2175.
29. Lippman SM, Lotan R. Advances in the development of retinoids and chemo preventive agents. Journal of Nutrition 2000;1307:4795-4825.
30. Vokes CE, Weichselbaum RR, Lipmans M, Hong WK. head and neck cancer (review article). New England Journal of Medicine. 1993;328:184-194.
31. Squier CA,Cox P, Hall BK. Enhanced penetration of Nitrosonornicotine across oral mucosa in the presence of ethanol. Journl Oral Pathol. 1986;15(5):276-269.
32. Brunaud L, Alberto JM, Avau A, Gerenava P, Namour F, Antunes L. Effects if Vitamin B12 and Folate defiviency on DNA methylation and carcinogenesis in rat liver. Cli Chem Lab Med 2003;41(8):1012-1019.
33. Rania H, Yosra B, Asma O-K, et al. Plummer-Vinson syndrome. La Tunisie Medicale. 2010;88(10):721-724.
34. Vinson PO. Hysterical dysphagia. Minn Med 1922;5:207-108.
35. Larson LG, Sandstron A, Westhind. Relationship of Plummer-Vinson disease to cancer of the Upper Alimentary Tract in Sweden. Cancer Research 1975;35:3308-3316.
36. Ahlbon HE- Simple Achlorhydric Anemia, Plummer-Vinson Syndrome and cancer of the mouth, pharynx, and esophagus in women, Brit Med J 1936;2:231-233.
37. Ribeiro U, Posner MC, Safat le-Ribeiro AV, et al. Risk factor for squamous cell carcinoma of the oesopahgus. Br J surg. 1996;83:1174-1185.
38. Marcland JL, Luce D, Leclerc A, et al. Laryngeal and hypopharyngeal cancer and occupational exposition to asbestos and man-made vitreous fiber: results of a case-control study. Am J Ind Med. 2000;37(6):581-589.

39. Berrino F, Richiardi L, Boffetta P, et al. Occupation and larynx and hypopharynx cancer: a job exposure matrix approach in an international case-control study in France, Italy, Spain, and Switzerland. Cancer Causes Control. 2003;14:213-223.
40. Formaldehyde. Reports on Carcinogens 2011;12.
41. Liu YR, Zhou Y, Qui W, et al. Exposure to formaldehyde induced heritable DNA mutations in mice. Toxicol Environ Health A. 2009;72(11):767-773.
42. Wang M, Cheng G, Bolbo S, Carmella SG, Villalta PW, Hecht SS. Clear difference in levels of a formaldehyde DNA adduct in leucocytes of smokers and none smokers. Cancer Research 2009;69(18):7170-7174.
43. Toyokani S. Mechanisms of asbestos-induced carcinogenesis. Nagoya J med 2009; 71:1-10.
44. Stafford ND. Aetiology of head and neck cancer: Cancer as a genetic disease. In Scott's Brown Orolaryngology, Head and Neck Surgery 7th Ed. Vol 2 Ch 180 p2351-2358
45. Canto MT, Devesa SS. Oral cavity cancer incidence rates in the United States, 1975 -1988. Oral Oncol 2002;38:610-617.
46. Hoffman HT, Karnell LH, Funk GF, et al. National cancer Database report on the head and neck. Arch Otolaryngol Head and neck surgery 1998;124:951-962.
47. Cancer Clinical Practice guideline (oncoline), Head and neck cancer: Hypopharyngealcancer.Availableonhttp://www.oncoline/headandneck/hypopharyngeal..
48. Wahid FI, Hussain M, Khan A, Khan IA. Frequency of hypopharyngeal carcinoma in patients presenting with dysphagia. Pak J Surg 2012;28(1):17-20.
49. Blot WJ, McLaughlin JK, Winn DM, Austin DT, et al. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res. 1998 June;48(11):3282-3287.
50. Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th Ed. New York, NY: Springer, 2010, pp 41-56.
51. Bosetti C, Negri E, Franceschi S, et al. Risk for oral and pharyngeal cancer in women: a study in Italy and Switzerland. Br J Cancer. 2000;82(1):204-207
52. Doll P, Reto R, Boreham J, Sutherland I. Mortality from cancer in relation to smoking; 50year observation on British doctors. Br J Cancer. 2005 Feb;92(3):426-429.

53. Takezaki T, Shinoda M, Hatooka S, et al. Subsite specific factor for hypopharyngeal and esophageal cancer, Japan. Cancer Causes Control. 2000;11(7):597-608.
54. Laforest L, Luce D, Golberg P, et al. Laryngeal and hypopharyngeal cancer and occupational exposure to Formaldehyde and various dusts; a case-control study in France. Occup Envirom Med. 2000;57(11):767-73.
55. Franseschi S, Bidori E, Barvon AE, et al. Maize and risk of cancers of the oral cavity, pharynx and oesophagus in Northern Italy. Journ Nat Cancer Inst, 1990;82(17):1407-1411.
56. Onyango JF, Awange DO, Njiru A, Macharia IM. Pattern of occurrence of head and neck cancer presenting at Kenyatta Hospital, Nairobi. East Africa Medical Journal 2006;83(5):288-291.
57. National Institute of Alcohol Abuse and Alcoholism.
Available on www.niaaa.hih.gov/
58. Swoboda H, Neumann H, Cartellieri M. Changes in the age of illness onset in cancer of the hypopharynx and larynx since 1960: The epidemiologic context in Austria. HNO 1989;37(3):85-91.
59. Cooper MP, Jovanovic A, Nauth JJ et al, Role of genetics in the etiology of squamous cell carcinoma of the head and neck. Arch Otolaryngol head Neck Surge 1995;121(2):157-160.
60. Mishra A, Sihgn VP, Verma V. Enviromental effects on head and neck cancer in India. J Clin Oncol 2009;27:15s: e17059.
61. Dequanter D, Lothaire P, Zovaoui K, Brohèe D. Epidemiology and clinical characteristics of larynx and hypopharynx carcinoma: comparative study in Hainaut and review of the literature. Acta Clin Belg 2012;112(6):423-425.
62. Milisavljevic D, Stankovic M, Zivic M, et al. Factors affecting results of treatment of hypopharyngeal carcinoma. Hippokratia 2009;13:154-160.
63. Hall SF, Groome PA, Irish J, Sullivan BA. Natural history of patient with squamous cell carcinoma of the hypopharynx. Laryngoscope 2008;118:1362-1371.
64. Wynder EL, Hultberg S, Jacobsson F, et al.: Environmental factors in cancer of the upper alimentary tract; a Swedish study with special reference to Plummer-Vinson (Paterson-Kelly) syndrome. Cancer 1957. 10 (3): 470-87.

65. Kenya Demographics and Health Survey (KDHS) 2008-2009.
66. Pavord S, Myers B, Robinson S, Allard S, Strong S, Oppenheimer C. UK guidelines on the management of iron deficiency in pregnancy. British Committee for Standards in Haematology (BCSH). 2011.
67. Uzcudum EA, Retolaza IR, Grande AG, et al. Pharyngeal cancer prevention: evidence from a case control-study involving 232 consecutive patients. J Laryngol Otol 2002.116(7);523-531.
68. Clapp RW, Jacobs MM, Loechler EL. Enviromental and occupational causes of cancer New Evidence 2005. Rev Environ Health 2008;23(1):1-37.
69. Anon In Marsabit, water blamed for cancer. Sunday Nation March 29th, 2009.
70. "Monographs on the evaluation of the carcinogenic risk of chemicals to humans," in Indoor Air Pollution from Heating and Cooking: Some Solid Fuels and Cooking Oil Fumes 95, vol. 95, IARC Press, Lyon, France, 2006.
71. Straif K, Baan R, Grosse Y, Secretan B, Ghissassi FE, and Cogliano V. "Carcinogenicity of household solid fuel combustion and of high-temperature frying." The Lancet Oncology, 2006. 7(12): 977–978.
72. Pan G,Takahashi K, Feng Y et al., "Nested case-control study of esophageal cancer in relation to occupational exposure to silica and other dusts," American Journal of Industrial Medicine, 1999.35: 272–280.
73. Sapkota A, Gajalakshmi V, Jetly DH et al., "Indoor air pollution from solid fuels and risk of hypopharyngeal/ laryngeal and lung cancers: a multicentric case—control study from India," International Journal of Epidemiology,2008.37(2):321–328.
74. Kushihashi Y, kadokura Y, Takiguchi A et al. Association between head and neck cancer and active passive cigarette smoking. Health 2012;4(9):619-624.
75. Parson A, Daley A, Begh R. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: Systemic review of observational studies with meta-analysis. BMJ 2010;340:5569.
76. Hashube M, Brennan P, Benhamou S. Alcohol drinking in never users of Tobacco, cigarette smoking in never drinkers and risk of head and neck cancer: Pooled analysis in International head and neck cancer. Epidemiology Consortium. JNCI 2007;99(10):777-789.

77. Riboli E, Norat T. Epidemiologic evidence of protective effect of fruits and vegetables. Am J Clin Nutr 2003;73(3):559S-569S.
78. Vainio H, Weiderpass E. “Fruit and vegetables in cancer prevention,” Nutrition and Cancer, 2006.54(1):111–142.
79. Pavia M, Pileggi C, Nobile CGA, Angelillo S. Association between fruit and vegetable consumption and oral cancer: Meta-analysis of observational studies. Am J Clin Nutr 2006;83(2):1126-1134.

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2nd August, 2013

Dr. Muturi Caroline Kirigo
Department of Surgery
School of Medicine
University of Nairobi.

Dear Dr. Muturi

RESEARCH PROPOSAL: CHARACTERISTICS OF PATIENTS WITH SQUAMOUS CELL CARCINOMA OF HYPOPHARYNX AT KENYATTA NATIONAL HOSPITAL (P72/02/2013)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 2nd August, 2013 to 1st August, 2014.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.

g) Submission of an *executive summary* report within 90 days upon completion of the study
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website **www.uonbi.ac.ke/activities/KNHUoN.**

Yours sincerely

PROF. M. L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. Prof. A.N. Guantai, Chairperson, KNH/UoN-ERC
The Deputy Director CS, KNH
AD, Health Information, KNH
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Supervisors: Prof. I. M. Macharia, Dr. J. K. Kamau