

**FACTORS ASSOCIATED WITH ESOPHAGEAL CANCER BY
ALTITUDE DIFFERENCES IN TANZANIA: A COMPARATIVE STUDY**

Jackson Rehman Matondo, MD

**MMed (Surgery) Dissertation
Muhimbili University of Health and Allied Sciences
October, 2021**

Muhimbili University of Health and Allied Sciences

Department of Surgery



**FACTORS ASSOCIATED WITH ESOPHAGEAL CANCER BY
ALTITUDE DIFFERENCES IN TANZANIA: A COMPARATIVE STUDY**

By

Jackson Rehmans Matondo

**A Dissertation Submitted in (Partial) Fulfillment of the Requirements of the Degree of
Master of Medicine (Surgery) of**

**Muhimbili University of Health and Allied Sciences
October, 2021**

CERTIFICATION

The undersigned certify he has read and hereby recommends for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled: **“Factors Associated with Esophageal Cancer by Altitude Differences in Tanzania: A Comparative Study”**, in (partial) fulfillment of the requirements for the Master of Medicine (Surgery) of Muhimbili University of Health and Allied Sciences (MUHAS).

Dr. Larry O. Akoko

(Supervisor)

Date

DECLARATION AND COPYRIGHT

I, **Dr. Jackson Matondo** declare that this **dissertation** is my original work and that it has not been presented and will not be presented to any other university for a similar or any other degree award.

Signature.....

Date.....

This dissertation is a copyright material protected under the Berne Convention, the Copyright Act 1999, and other international and national enactments, in that behalf, on intellectual property. It may not be reproduced by any means, in full or in part, except for short extracts in fair dealing, for research or private study, critical scholarly review or discourse with an acknowledgment, without written permission of the Directorate of Postgraduate Studies, on behalf of both the author and the Muhimbili University of Health and Allied Sciences.

ACKNOWLEDGMENT

I thank the Almighty God for the gift of life, good health, and wellbeing to be able to accomplish this research.

I would like to express my sincere appreciation to my supervisor and mentor, Dr. Akoko for guidance through each stage of this study.

I am thankful to MUHAS, ORCI, and MNH Staffs, who took part in this study by providing outstanding support and help where needed during my dissertation research work, particularly during data collections.

Lastly, I would like to thank Dr. Chamshama, Dr. Alexander, and Dr. Mohamed at MNH surgical department for encouragement and support during the research.

DEDICATION

This dissertation is dedicated to my wife and children without whom this work would not be worthy of the efforts.

ABSTRACT

Background: Esophageal cancer is the 8th most common cancer and the 6th cause of cancer deaths in the world. There is a discrepancy in the distribution of the disease in highlands and lowlands. In Tanzania, there is a trend that shows the prevalence of the disease is increasing in lowlands. This change seems to be due to the bias of some risk factors that have become more common in lowlands. However, there is no current information in Tanzania on the distribution of risk factors for esophageal cancer between lowlands and highlands.

Aim of the study: Is to compare the occurrence of risk factors between EC patients coming from lowlands with those coming from highlands

Methodology: A prospective comparative hospital-based study was conducted among patients at Muhimbili National Hospital and Ocean Road Cancer Institute. The subjects were categorized into groups of those coming from highland areas and those coming from lowland areas. Information on demography and risk factors for esophageal CA was collected. The data was then analyzed to calculate the Odds ratios of the presence of individual risk factors in low land areas compared to highland areas.

Results: A total of 310 participants were enrolled in the study. There were 136 participants from the lowlands and 174 from highlands. The mean age of participants was 57.4 ± 14.5 years. Squamous cell carcinoma was the most common histological type in both lowlands and highlands. Patients from highlands had 1.9 odds of drinking alcohol compared to patients from lowlands (p-value 0.006, CI 1.2 – 3.1). The commonest risk factors in lowlands were drinking hot beverages at 97.8% while the commonest risk factor in highlands was the consumption of red meat (97.7%).

Conclusions: In Tanzania, esophageal cancer is still a predominantly a highlands disease however the incidence in lowlands is on the rise. Most of the risk factors profiles do not differ significantly between patients from highlands and lowlands except alcohol intake and red meat consumption which are more common in highlands and taking of hot drinks which is most common in lowlands.

TABLE OF CONTENTS

CERTIFICATION	i
DECLARATION AND COPYRIGHT	ii
ACKNOWLEDGMENT	iii
DEDICATION	iv
ABSTRACT	v
TABLE OF CONTENTS	vi
LIST OF TABLES	viii
LIST OF FIGURES	ix
ACRONYMS AND ABBREVIATIONS.....	x
OPERATIONAL TERMS	xi
CHAPTER ONE.....	1
1.0 INTRODUCTION	1
1.1 Background.....	1
1.2 Literature Review	3
1.3 Problem Statement.....	5
1.4 Rationale	5
1.5 Research Hypothesis.....	5
1.6 Conceptual framework.....	6
1.7 Objectives	7
1.7.1 Broad Objective.....	7
1.7.2 Specific Objectives.....	7
CHAPTER TWO.....	8
2.0 METHODOLOGY	8
2.1 Study design.....	8
2.2 Study Area	8
2.3 Study population	8
2.4 Inclusion and exclusion criteria	9
2.4.1 Inclusion criteria.....	9

2.4.1 Exclusion criteria.....	9
2.5 Sample size	9
2.6 Study Variables.....	9
2.7 Data collection method	9
2.8 Data management	10
2.9 Data analysis	10
2.10 Ethical consideration.....	11
2.11 Study limitations and mitigation.....	11
2.12 Results dissemination	12
CHAPTER THREE	13
3.0 RESULTS.....	13
CHAPTER FOUR	18
4.0 DISCUSSION.....	18
CHAPTER FIVE	20
5.0 CONCLUSION AND RECOMMENDATIONS	20
5.1 Conclusions.....	20
5.2 Recommendations.....	20
REFERENCES	21
APPENDICES	24
Appendix I: Informed Consent (English version).....	24
Appendix II: Questionnaire (English version).....	26
Appendix III: Informed Consent (Swahili version).....	30
Appendix IV: Questionnaire (Swahili Version)	32

LIST OF TABLES

Table 1: Social demographics of patients with esophageal cancer treated at MNH in 2019/2020. 14

Table 2: Association between various known risk factors for esophageal cancer by comparing between lowlands and highlands in Tanzania 17

LIST OF FIGURES

Figure 1: Conceptual framework.....6

Figure 2: Columns showing distribution of patients with EC from lowlands treated at MNH between 2019/2020..... 15

Figure 3: Columns showing distribution of patients with EC from highlands treated at MNH between 2019/2020..... 15

Figure 4: Columns showing the histological distribution of EC between lowlands and highlands patients at MNH between 2019/2020..... 16

ACRONYMS AND ABBREVIATIONS

AIDS	-	Acquired Immunodeficiency syndrome
EC	-	Esophageal Cancer
CI	-	Confidence Interval
GERD	-	Gastroesophageal Reflux Disease
HIV	-	Human immunodeficiency Virus
IRB	-	Institution Review Board
LMIC	-	Low and middle-income countries
MNH	-	Muhimbili National Hospital
MoHCDGEC	-	Ministry of Health, Community Development, Gender, Elderly and Children
MR	-	Medical Records
MUHAS	-	Muhimbili University of Health and Allied Sciences
NBS	-	National Bureau of Statistics of Tanzania
ORCI	-	Ocean Road Cancer Institute
SPSS	-	Statistical Package for the Social Sciences
WHO	-	World Health Organization

OPERATIONAL TERMS

1. GPS Geographical positioning system, an internet application that is used to identify a location on the earth's surface. It can show geographical features of a certain place such as altitude from the sea level, longitude, and latitude.
2. Lowland; - In physical geography, a lowland is any broad expanse of land with general low elevation.
3. Highlands are any mountainous region or elevated mountainous plateaus, they are generally considered to be land above 500metres from sea level.
4. Oesophagoscopy is a procedure in which a flexible/ rigid endoscopy is inserted through the mouth or more rarely through the nose and into the esophagus. The procedure allows visualization of esophageal mucosa from the upper esophageal sphincter to the esophagogastric junctions.
5. Tanzania coastal zone is the group of administration regions along the coastal belt of Tanzania which includes Tanga, Dar es Salaam, Morogoro, Pwani, Lindi, and Mtwara.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Esophageal cancer (EC) is the eighth most common cancer in the world and the sixth leading cause of death from cancer in the world(1).This is the only cancer that is recording an increasing incidence all over the world despite the treatment modalities currently available for the management of this disease (2). The rate of new cases in the world in 2012 was 455800 cases (1). The highest incidence of esophageal cancer is seen in two geographical belts, one from north-central China through the central Asian republics to northern Iran, and the other from eastern to southern Africa (3,4). The low incidence rate has been identified in the western part of Africa, central Africa, Central America, and North America (3). This variation also exists within a country with areas of high incidence and those of low incidence.

EC variations are also seen with the major histological types where Adenocarcinoma (AC) is more common in High-Income countries (HICs) while Esophageal Squamous Cell Carcinoma (ESCC) is more prevalent in Low- and Middle-Income countries. The existence of geographical difference shows that ethnicity, genetic factor, and lifestyle all play a role in the development of Esophageal cancer(2,5).

Esophageal Cancer ranks as the sixth most common cause of death among cancers (4,6). Squamous cell carcinoma remains predominant, as 80% of death are due to this type of Esophageal cancer (4). In 2012, 16,000 deaths due to Esophageal cancer was expected (1). The disease has a 5-year survival rate of less than 20% (1,6,7), making it the most lethal disease despite advances in medical services.

Risk factors for esophageal cancer are demographic factors (gender, race, age, and living area), genetics, previous medical conditions (gastroesophageal reflux disease, obesity, and esophageal diseases), chemical exposure (polycyclic aromatic, hydrocarbon, tobacco smoking, and alcohol intake) and diet (red meat and hot coffee/ tea drink)(1–6,8).

Some risk factors are common to both lowland and highland areas (e.g. age, gender) while others do differ according to geographical distributions (e.g. race, chemical exposure, diet, low social economic status(9) (9 - 12).

East African countries are among the countries with the highest rate of esophageal cancer. Kenya is the third most common country while Uganda and Tanzania rank at eighth and twelfth respectively (10). In 2018 the incidence of esophageal cancer in Tanzania was 6.7 per 100000 population (10).

In Tanzania, esophageal cancer was more observed in patients coming from highlands. However, the cause of higher incidence in highlands compared to the lowlands of Tanzania remains unknown. There are suggestions that there exists a difference in the distribution of risk factors between the lowlands and highlands. However, that discrepancy is not well documented in Tanzania.

1.2 Literature Review

The incidence of esophageal cancer in most countries is higher in highlands than in lowlands. This is true in many studies such as that done in China by Yu Y, et al (11), in which Linxian being the mountainous region in China has a high Esophageal cancer rate in the country than any other place. This is different from studies carried out in East Africa where most patients were seen to originate from lowlands (12,13).

Risk factors of Esophageal Cancer

Tobacco smoking

Smoking is the main risk factor for esophageal squamous cell carcinoma with an increasing factor five times compared to non-smoker(1). In Tanzania, there is a high percentage of tobacco smoking in highlands when compared to lowland (14). Therefore, through this observation, EC is expected to be high in highland than in lowland.

Alcohol

Alcohol is also one of the main risk factors of Squamous Cell Carcinoma, relative risk increases with an increase in alcohol intake(15). In Tanzania, highlands have higher alcohol consumption than lowlands. Reports show in 2014 Hai and Morogoro had 47.3% and 14.7% respectively of daily male drinkers, while the lowland regions such as Dar es Salaam had 6.2%(15). This might be attributed to the difference in culture between the two areas. In Kilimanjaro (highland), they have a cultural practice of drinking local alcohol in different traditional ceremonies.

Polycyclic aromatic compounds

These are known carcinogenic materials created during the incomplete burning of wood, so preservation of food using smoke increases the risk of EC mostly in developing countries including Tanzania (16,17). Apart from a few urban centers in Tanzania, there is no much more difference in terms of food preservative measures between the lowland and highland, since the majority of Tanzanians preserve food traditionally.

Social demographical factors

Squamous Cell Carcinoma is common in black men and white women while Adenocarcinoma is common in White men, EC risks increase with an increase in age (18). Most of the social demographic risk factors are distributed equally among the Tanzanian's lowland and highland. EC due to geographical (altitude) distribution is not known in Tanzania, but this study will investigate the discrepancy in terms of EC risks between lowland and highland.

Tylosis

This genetic condition presents with hyperkeratosis of palm/soles which is strongly associated with SCC (1). The condition doesn't show distribution between highlands and lowlands in studies done in America (19), Germany(20), and Finland (13). There is no study done in Tanzania to determine these genetic conditions in our society.

Diet

High consumption of processed red meat is associated with an increased rate of EC but is considered after several mechanisms(1). Hot coffee/tea is implicated to increase the risk of EC but there is little evidence about the rate of use and development of esophageal cancer (1,16). Tanzania is among the LMICs where the incidence of EC is high because of low levels of vitamins and minerals resulting from low consumptions of vegetables and fruits, particularly in urban areas where there is an increase in consumption of processed food(18).

In Tanzania, there is an increase in the use of processed meat particularly in big cities such as Dar es Salaam and Tanga, also according to the Tanzania Coffee Board (TCB), coffee consumption is increasing in urban and semi-urban, more in the coastal areas(21). Since many studies have found an increased rate of esophageal adenocarcinoma with a western-style diet (high in meat consumption and low in vitamins and minerals (22).

Previous medical conditions

A patient with a history of partial gastrectomy has a relative increased risk more than two times compared to others(1). There is no known data about the difference in the incidence of these risk factors among the lowland and highland areas.

1.3 Problem Statement

Esophageal cancer has been known as a disease more common in highlands. This has been attributed to the difference in distribution of risk factors between highlands and lowlands. Recent studies in Tanzania shows esophageal cancer is on the rise in lowlands (3). This suggests a change in the distribution of risk factors between highlands and lowlands. However, this new distribution of risk factors has not been documented hence there is no current information of the distribution of risk factors of esophageal cancer in Tanzania.

1.4 Rationale

Understanding the epidemiological differences in esophageal cancer between lowlands and highlands in Tanzania will help in designing risk factor studies as there is a possibility of differences in risk factor profiles among these patients. Preventive measures for EC cancer will therefore be directed according to the region of residence based on altitudes. The study will further help in properly identifying high-risk regions in the country thereby helping with the targeting of resources to where they are needed.

1.5 Research Hypothesis

1. Null Hypothesis (H_0)

There is no difference in distribution of risk factors of esophageal cancer between highlands and lowlands.

2. Alternative Hypothesis (H_1)

There is a difference in distribution of risk factors of esophageal cancer between highlands and lowlands.

1.6 Conceptual framework

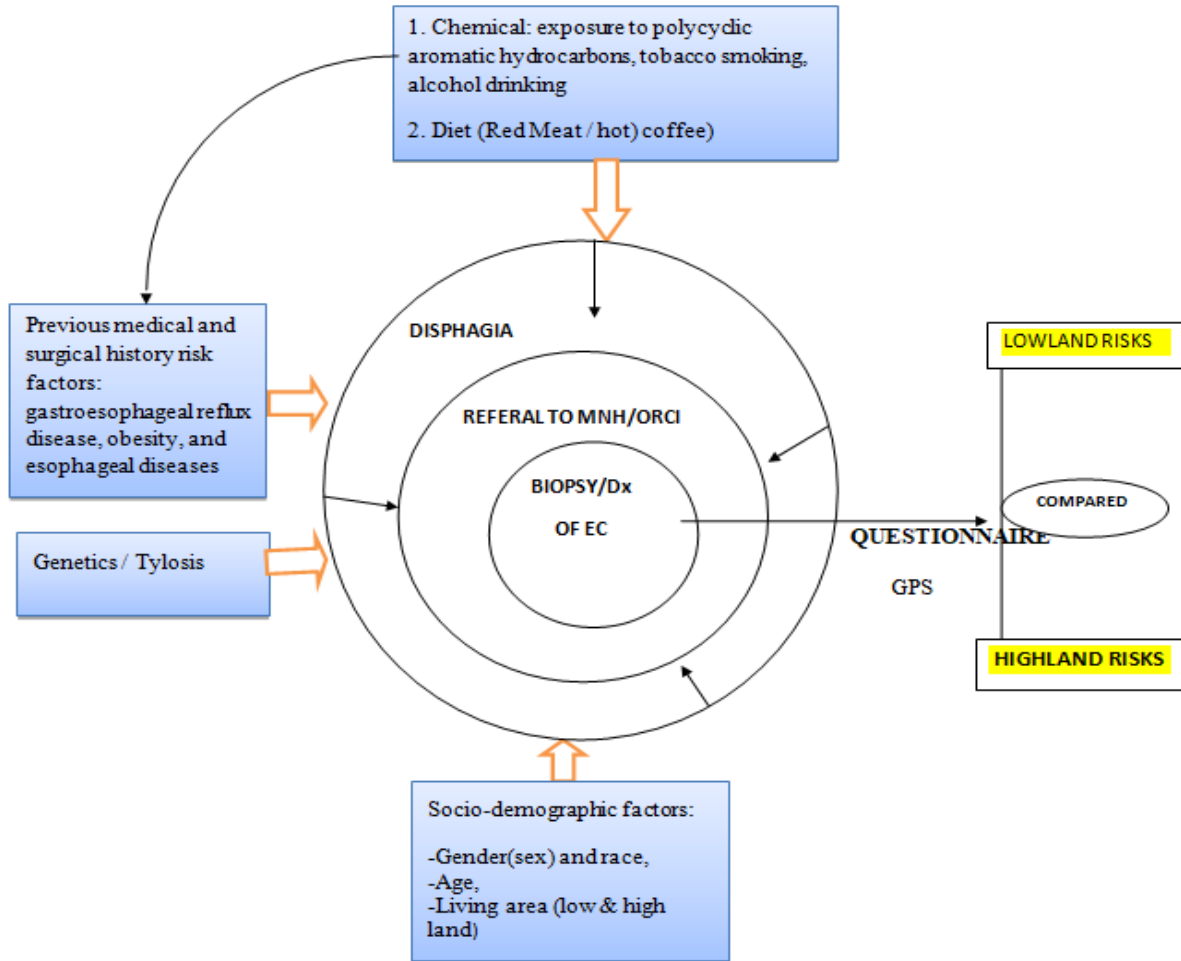


Figure 1: Conceptual framework

1.7 Objectives

1.7.1 Broad Objective

To compare the occurrence of risk factors between EC patients coming from lowlands with those coming from highlands.

1.7.2 Specific Objectives

- i. To estimate the proportion of esophageal carcinoma attributed to lowland residency.
- ii. To compare the distribution of risk factors between EC patients from lowlands with those from highlands
- iii. To determine the predominant risk factor characteristic of each group

CHAPTER TWO

2.0 METHODOLOGY

2.1 Study design

This was a hospital-based prospective comparative study was carried out From May 2019 to January 2020.

2.2 Study Area

The study was conducted at Muhimbili National Hospital (MNH) and Ocean Road Cancer Institute (ORCI), which both are the main referral centers for EC in the country: MNH has a diagnostic capacity that includes endoscopy and histology services, while ORCI has chemotherapy, radiotherapy, and palliative care services. With the lack of radiation services in both highland regions, almost all patients are going to be referred to Dar es Salaam where the two hospitals are located. Therefore, this was an ideal location for a faster and cost-effective way to recruit patients. Annually, over 200 patients with histological diagnosis of EC are seen at MNH, with most recent studies suggesting over 50% are from the lowlands, especially the coastal belt such as Tanga, Coastal region, Lindi, and Dar es Salaam. MNH has both medical and surgical endoscopy teams both running OPD services as well with EC patients seen by either of the teams. At ORCI, there is a daily clinic serving EC patients. Some of the patients at ORCI would have been seen at MNH already.

2.3 Study population

The study population is comprised of all gastroenterology OPD cases and surgical inpatients at MNH and ORCI.

2.4 Inclusion and exclusion criteria

2.4.1 Inclusion criteria

- i. Adult patient aged more than 18 years,
- ii. Patient with a histological diagnosis of EC
- iii. Patients whose time of stay in either lowland or highland exceed ten years,
- iv. Consented to participate

2.4.1 Exclusion criteria

- i. Patients who are unable to express themselves in Kiswahili or English.

2.5 Sample size

Initially, this study was designed to recruit 74 patients in each arm. But due to ease of accrual of patients, we managed to recruit 136 cases in the lowlands and 174 patients in the highlands, this study had a power of 80% to detect an effect size of 0.322 at type 1 error of 5%(23).

2.6 Study Variables

Independent variable: Lowland versus Highland

Dependent variables: social demographic factors (gender, race, and age), genetics, previous medical conditions (gastroesophageal reflux disease, obesity, and esophageal diseases), chemical exposure (polycyclic aromatic, hydrocarbon, tobacco smoking, and alcohol intake), and diet (red meat and hot coffee/ tea drink)

2.7 Data collection method

Daily admissions and OPD gastroenterology (including endoscopy suite) at MNH were checked for patients with a diagnosis of EC. The same was undertaken at ORCI. Two research assistants were used, one at MNH and the other at ORCI. Eligibility to participate was checked using an eligibility questionnaire. For those eligible, consent to participate was then obtained and a pre-defined study questionnaire was administered.

The participants' address was recorder from the level of ward, district and regions. The name of the ward was then entered into a mapping website, elevationmap.net that used a Light Detection and Ranging (LIDAR) system to determine the elevation from sea level. The LIDAR system can detect the elevation on the earth's surface to the accuracy of 15 cm (24). The generated altitude data was extracted from the system. The altitude was thereafter classified from 0 to 500m as low lands and above 500m was classified as highlands.

Thereafter a questionnaire with structured question was administered to the study participants. The sex of the patient was documented as the biological sex. Age was obtained from subtracting the patients' date of birth to the date of the interview and was recorded in years. Information on the risk factors was recorded as being present or being absent.

2.8 Data management

Collected data was checked for competences, coded, and entered into SPSS software version 24 for storage and subsequent analysis. Categorical variables were summarized in tables, while continuous variables were summarized into means and standard deviations.

2.9 Data analysis

Data analysis was done using the chi-square test and Fisher exact test that was used to determine the proportion of EC attributed either to lowland or higher land residence, then the distribution of EC risk factors was compared between lowland and highland. Finally, the EC risk factor having the highest frequency was determined. Significance was considered when the p-value was less than 5% (0.05).

To estimate the proportion of esophageal carcinoma attributed to lowland residency. This was obtained by taking the number of patients with esophageal cancer in the research from the lowland when compared to those from highland in the same duration of time.

To compare the distribution of risk factors between EC patients from lowland with those from highland

- i. Here the frequency of each risk factor in each group was obtained

- ii. There was a comparison of each risk factors frequencies in each group
- iii. In each risk factors comparison those with a p-value less than 5%, was considered statistically significant

To determine the predominant risk factor characteristics of each group

- i. In each group, the risk factor with many frequency occurrences was taken and cross-tabled with different characters such as histological results of esophageal cancer, occupation, sex, and age.
- ii. In all characters, the p-value was obtained, and it was considered statistically significant if less than 5%.

2.10 Ethical consideration

Ethical clearance was sought from MUHAS IRB. Permission to conduct the study was sought from MNH and ORCI authority. Written informed consent was obtained from the participants before the interview. The participants had the right to withdraw from the study at any time after the start of the interview. The study imposed minimum risk to participants. The study did not interfere with the care offered to patients and interviews were conducted when no care was planned. All of the participants' information was kept confidential. All the research data, software, and hardcopies that were used in the study were handled to MUHAS authority after the study for publication.

2.11 Study limitations and mitigation

- i. The study was located in the lowland which will lead to more patients in the lowlands to be accessible compared to highland. Two fixed sample size from each population was used.
- ii. Recall bias such as some of the risk factors occurred many years ago. Each patient was given enough time to memorize the past events, even to reschedule the interview
- iii. The study is a hospital-based study (only referred patient), those not referred to Muhimbili National Hospital and Ocean Road Cancer Institute will not get the chance

to be enrolled in the study. The study maximized the sample size to enroll many patients from the referred hospitals, and hence minimize errors.

2.12 Results dissemination

The finding of the study was presented to the department of surgery MNH, and at local and international conferences. Similarly, publication in regional or international journals will be done, hard and soft copies will be made available to the department and University library for the deposit into the repository.

CHAPTER THREE

3.0 RESULTS

During the study period of six months, 310 patients with EC were managed at MNH and ORCI. In Table 1 we present the sociodemographic features of the above patients. Their mean age was 57.4 ± 14.5 years (26 – 84) years with most patients in the age group between 40 – 60 years at 136(43%) followed by those between 60 – 80 years at 107(34.5%) and <40 years at 48(15.5%). Male patients were the majority at 269(86.8%) giving a male to female ratio of 6:1. Most EC patients: had less than seven years of education, were low land residents, were peasants, and were married at 205(66.1%), 174 (56.1%), 149(48.1%) and 206(66.5%) respectively.

Table 1: Social demographics of patients with esophageal cancer treated at MNH in 2019/2020.

Variable	Frequency (%)
Sex	
Male	269 (86.8)
Female	41 (13.2)
Age (years)	
< 40	48 (15.5)
40 – 60	136 (43.9)
60 – 80	107 (34.5)
> 80	19 (6.1)
Years of Education	
≤ 7	205 (66.1)
7 – 11	54 (17.4)
>11	6 (1.9)
Residency altitude	
Lowlands	136 (43.9)
Highlands	174 (56.1)
Occupations	
Agriculture	149 (48.1)
Business	54 (17.4)
Formal Employment	31 (10.0)
Unemployed	76 (22.9)
Marital status	
Not married	20 (6.5)
Married	206 (66.5)
Cohabiting	30 (9.7)
Widow/widower	37 (11.9)
Divorced	17 (5.5)

In Figure 2 and 3, we present the districts of domicile of patients with EC treated from around Tanzania. We further segregate them into either lowland residency or highland residency basing on altitude from sea level as stated in the methodology section. In Figure 2, we present patients from lowlands with the others category comprising patients from 169 districts.

Most patients had residency in Temeke district at 23(17%) followed by Ilala and Tanga urban at 20(15%) and 15(11%) respectively. In Figure 3, we present patients from highlands in which most patients were from Moshi at 25(14%) followed by Iringa and Mbeya at 13(8%) and 12(7%) respectively. The category with others comprised of patients from 154 districts.

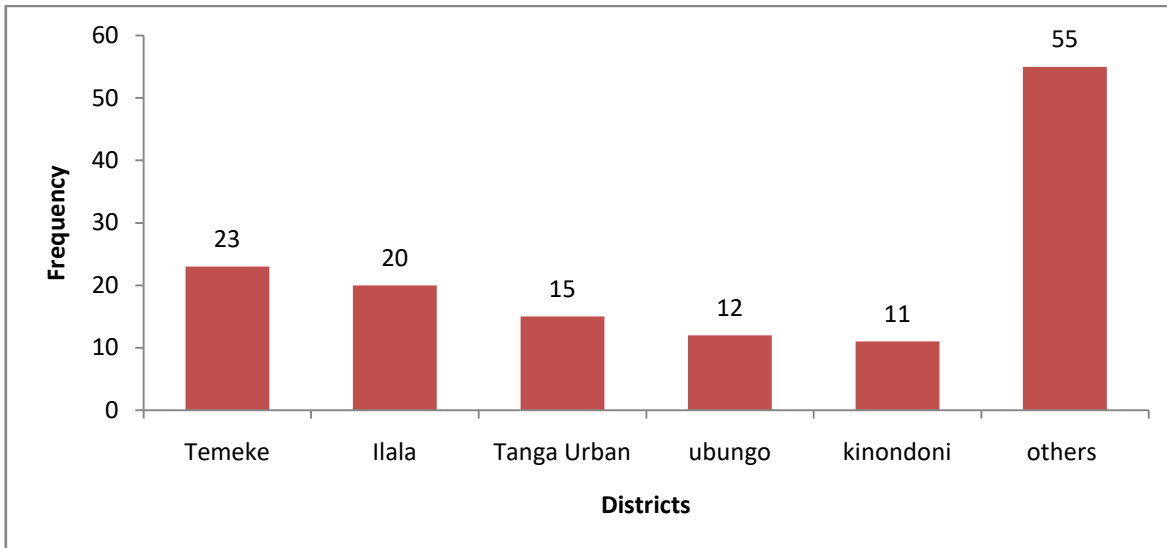


Figure 2: Columns showing distribution of patients with EC from lowlands treated at MNH between 2019/2020.

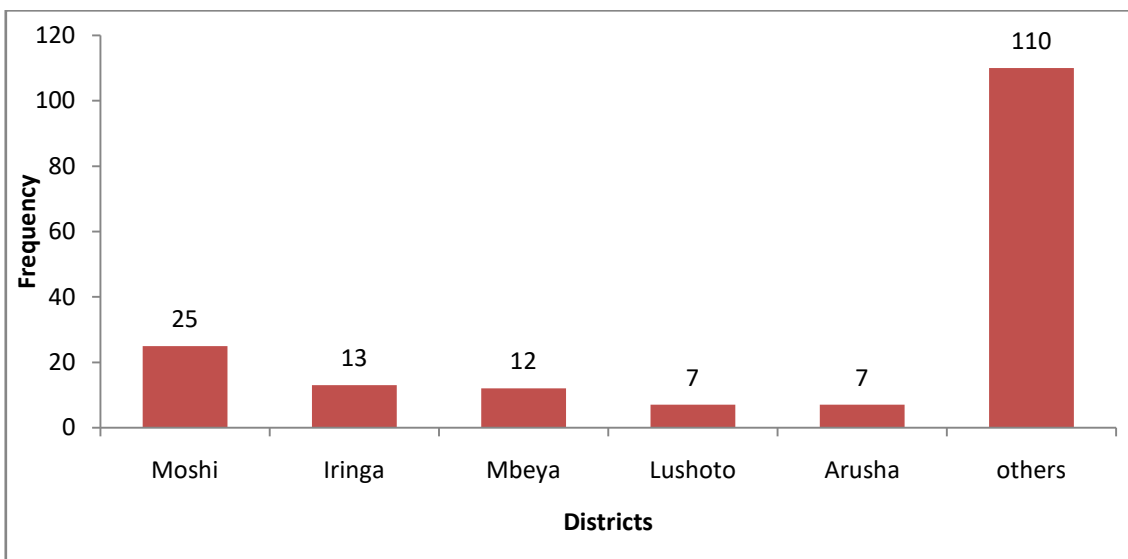


Figure 3: Columns showing distribution of patients with EC from highlands treated at MNH between 2019/2020.

In Figure 4 we compare the histological distribution of EC as either adenocarcinoma (ADC) or squamous cell carcinoma (SCC). There were 2% more ADC in the lowland patients compared to highland patients but the difference failed to reach significant levels ($p = 0.44$)

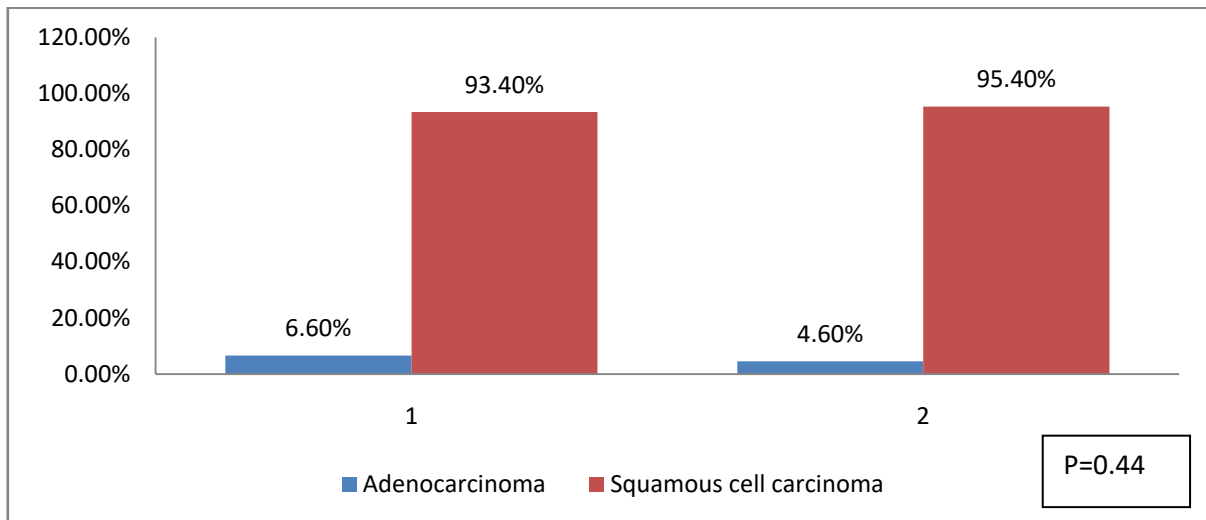


Figure 4: Columns showing the histological distribution of EC between lowlands and highlands patients at MNH between 2019/2020.

In Table 2 we show there was 15.5% more alcohol intake in highlands compared to lowlands ($p=0.006$; C.I. 1.2 – 3.1). Active tobacco smoking was 3.8% more common in lowlands compared to highlands. However this was not statistically significant ($p = 0.409$). Consumption of red meat was more common in highlands by 6.6% ($p = 0.01$). There was 5.2% more drinking of hot beverages in lowlands compared to highlands. ($p = 0.038$). Age groups, family history of esophageal cancer, history of obesity, HIV status, and previous abdominal surgery had some predominance among patients from highlands but failed to be statistically significant. While, heartburn, other reported esophageal conditions, and corrosive intake had predominance among low land but failed to be significant.

Table 2: Association between various known risk factors for esophageal cancer by comparing between lowlands and highlands in Tanzania

Risk factors	Lowland	Highland	P-value	OR	95%CI
Age group (yrs)					
<40	25 (18.4)	23 (13.2%)	0.12	1.23	0.42 – 1.48
40-60	59 (43.4%)	77 (44.3%)			
60-80	48 (35.3%)	59 (33.9%)			
>80	4 (2.9%)	15 (8.6%)			
Familial cancer					
Yes	7 (5.1%)	12 (6.9%)	0.524	1.36	0.5 – 3.6
No	129 (94.8%)	162 (93.1%)			
History of obesity					
Yes	61 (44.6%)	85 (48.9%)	0.49	1.21	0.8 – 1.8
No	75 (55.4%)	89(51.1%)			
HIV status					
Positive	9 (6.6%)	8 (4.6%)	0.634	0.68	0.2– 1.8
Negative	113 (83.1%)	151(86.8%)			
Active Smoking					
Yes	31 (22.8%)	33 (19.0%)	0.409	0.79	0.5 – 1.3
No	105 (77.2%)	141 (81.0%)			
Alcohol intake					
Yes	68 (50.0%)	114 (65.5%)	0.006	1.90	1.2 – 3.1
No	68 (50.0%)	60 (34.5%)			
Hot drinks					
Yes	133 (97.8%)	161 (92.5%)	0.038	0.3	0.07 – 1.0
No	3(2.2%)	13 (7.5%)			
Corrosive ingestion					
Yes	5 (3.7%)	2 (1.1%)	0.137	0.31	0.1 – 1.6
No	131 (96.3%)	172 (98.9%)			
History of heartburn					
Yes	71 (52.2%)	97 (55.7%)	0.535	1.15	0.7 – 1.8
No	65 (47.8)	77 (44.3%)			
Other esophageal diseases					
Yes	8 (5.9 %)	11 (6.3%)	0.87	1.08	0.4 – 2.8
No	128 (94.1%)	163 (93.7%)			
Red meat consumption					
Yes	124 (91.1%)	170 (97.7%)	0.01	4.1	1.3 – 13.1
No	12 (8.8%)	4 (2.3%)			

CHAPTER FOUR

4.0 DISCUSSION

Esophageal cancer in Tanzania has drawn considerable interest among researchers over the years. Initial attention was directed to highlands where most of the patients were coming from. This study has attempted to investigate the discrepancy of risk factors between highlands and lowlands in Tanzania.

We report a predominance of patients coming from Highlands who had EC in Tanzania. The mean age of EC patients was similar to that reported from Kenya and Ghana (25)(2). Furthermore, there was no significant difference in age groups of patients by altitude. In both highlands and lowlands, the predominant type of esophageal cancer was squamous cell carcinoma indicating similar etiological factors in those regions. However, there was a slight predominance of some factors in one region which will need further scrutiny to properly define the risk in altitudinal differences. This study was set following an initial study that had suggested that most patients were from lowlands (3). The error in misplacing the patients was a result of health-seeking behavior by patients who did not disclose properly their real residency for hospital costing logistics. We in this study considered residency a location where the patient had spent at least 10 years. We can now confidently conclude that while there is an increase in the incidence of EC in lowlands, the disease is still prevalent in highlands.

Further misclassification into altitudes was based on assumption that the entire coastal region was lowland something that the use of GPS refuted. This resulted in the current classification of places originally considered lowlands into highlands. To correctly assign the level of altitude where patients' real residency is located, we found it necessary to group them by districts and not regions as was done previously. This largely led to the drop in proportion originally considered to be lowlands dwellers within regions like Morogoro and Tanga. Most of the common risk factors had remained the same except alcohol intake which was high in both altitudes but more predominant among high altitude dwellers.

In recent years, hot drinks have been evaluated for their possible causative role in EC due to chronic inflammation. A Kenyan study had validated tea temperature in a region with a high incidence of EC and noted that the temperatures were higher than in standard conditions(26). Drinking hot drinks increases the risk of EC due to damage in esophageal mucosa. We had postulated the increase of EC in the coastal region of Tanzania, initially grouped as lowlands, to be due to the hot coffee drinking habit most prevalent in the coastal community. Our study found that patients from lowlands were had greater odds of drinking hot drinks compared to highlands residents.

Esophageal diseases such as Barrett's esophagus and gastroesophageal reflux disease (GERD) are known to increase the risk of ADC and not ESCC(27). More patients with ADC of the esophagus were from highlands, though not significant. Further evaluation of these patients is needed to identify risk factors. Most of the patients who reported obesity had predominantly ADC which is consistent with other studies (28,29). People with HIV/AIDS face an overall increased risk for esophageal malignancy about 2.7 times higher than the general population(29). The HIV prevalence in our cohort represents the national prevalence of disease hence we do not think that HIV is a risk factor for EC.

CHAPTER FIVE

5.0 CONCLUSION AND RECOMMENDATIONS

5.1 Conclusions

- Esophageal cancer in Tanzania is still a predominantly highlands disease however the incidence of the disease in lowlands is on the rise.
- The commonest risk factor in lowlands is drinking hot beverages while the commonest risk factor in highlands is the consumption of red meat.
- The risk factor profile in these two altitudinal locations did not differ significantly except for alcohol intake and red meat consumption which were predominant in the high altitudes and taking of hot drinks which is predominant in lowlands.

5.2 Recommendations

- i. More researches should be done on the causal relationship between intake of hot drinks and the development of esophageal cancer in terms of the rate of use of hot drinks and the ideal temperature for the development of esophageal cancer.

REFERENCES

1. Otroshi O, Sadeghi-Gandomani H, Afshar M, Yousefi MS, Sharifi-Esfahani M, Pourgholam-Amiji N, et al. Esophageal cancer in the world: incidence, mortality and risk factors. *Biomed Res Ther.* 2018;5(7):2504–17.
2. Tettey M, Edwin F, Aniteye E, Sereboe L, Tamatey M, Ofosu-Appiah E, et al. The changing epidemiology of esophageal cancer in sub-Saharan Africa - The case of Ghana. Vol. 13, *Pan African Medical Journal. African Field Epidemiology Network*; 2012.
3. Mmbaga EJ, Deardorff K V., Mushi B, Mgisha W, Merritt M, Hiatt RA, et al. Characteristics of Esophageal Cancer Cases in Tanzania. *J Glob Oncol .* 2018 Nov
4. Abbas G, Krasna M. Overview of esophageal cancer. *Ann Cardiothorac Surg.* 2017 Mar
5. Huang F-L, Yu S-J. Esophageal cancer: Risk factors, genetic association, and treatment. *Asian J Surg.* 2018 May
6. Boyko V, Dubrovina N, Zamiatin P, Sinelnikov A, Gerrard R, Kolesnikova O, et al. Epidemiology and Forecast of the Prevalence of Esophageal Cancer in the Countries of Central and Eastern Europe. *J Adenocarcinoma* 2016 May 5
7. Pakzad R, Mohammadian-Hafshejani A, Khosravi B, Soltani S, Pakzad I, Mohammadian M, et al. The incidence and mortality of esophageal cancer and their relationship to development in Asia. *Ann Transl Med* 2016 Jan
8. Mir MM, Dar NA. Esophageal Cancer in Kashmir (India): An Enigma for Researchers. 2009;3(1):71–85.
9. Fan Y, Yuan JM, Wang R, Gao YT, Yu MC. Alcohol, tobacco, and diet in relation to esophageal cancer: The Shanghai cohort study. *Nutr Cancer.* 2008 May;60(3):354–63.
10. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA JA. Oesophageal cancer statistics | World Cancer Research Fund [Internet]. *CA cancer J Clin.* 2018

11. Yu Y, Taylor PR, Li J-Y, Dawsey SM, Wang G-Q, Guo W-D, et al. Retrospective cohort study of risk-factors for esophageal cancer in Linxian, People's Republic of China. *Cancer Causes Control*. 1993 May.
12. Hennies H-C, Hagedorn M, Reis A. Palmoplantar Keratoderma in Association with Carcinoma of the Esophagus Maps to Chromosome 17q Distal to the Keratin Gene Cluster. *Genomics*. 1995 Sep 1
13. Saarinen S, Vahteristo P, Lehtonen R, Aittomäki K, Launonen V, Kiviluoto T, et al. Analysis of a Finnish family confirms RHBDF2 mutations as the underlying factor in tylosis with esophageal cancer. *Fam Cancer*. 2012 Sep 26
14. Jagoe K, Edwards R, Mugusi F, Whiting D, Unwin N. Tobacco smoking in Tanzania, East Africa: Population based smoking prevalence using expired alveolar carbon monoxide as a validation tool. *Tob Control*. 2002 Sep;11(3):210–4.
15. Country Profiles African Region United Republic Of Tanzania (The) Recorded adult per capita consumption (age 15+) Total Beer Spirits Wine. 2004
16. Mir MM, Dar NA. Esophageal cancer in kashmir (India): an enigma for researchers. *Int J Health Sci (Qassim)*. 2009;3(1):71–85.
17. Patel K, Wakhisi J, Mining S, Mwangi A, Patel R. Esophageal Cancer , the Topmost Cancer at MTRH in the Rift Valley , Kenya , and Its Potential Risk Factors. 2013;
18. Chamberlain RM, Ngoma T, Soliman AS, Kahesa C, Mwaiselage J, Gabel J V, et al. Clinical and epidemiologic variations of esophageal cancer in Tanzania. *World J Gastrointest Oncol*. 2016;8(3):314.
19. Stevens HP. Linkage of an American Pedigree With Palmoplantar Keratoderma and Malignancy (Palmoplantar Ectodermal Dysplasia Type III) to 17q24. *Arch Dermatol*. 1996 Jun;132(6):640.
20. Hennies HC, Hagedorn M, Reis A. Palmoplantar keratoderma in association with carcinoma of the esophagus maps to chromosome 17q distal to the keratin gene cluster. *Genomics*. 1995 Sep;29(2):537–40.

21. USDA. Food and Agricultural Import Regulations and Standards - Narrative. 2013.
22. Dawsey SM, Fagundes RB, Jacobson BC, Kresty LA, Mallery SR, Paski S, et al. Diet and esophageal disease. *Ann N Y Acad Sci.* 2014 Sep
23. Jeffrey J. Walline. *Designing Clinical Research: an Epidemiologic Approach*, 2nd Ed. In: *Optometry and Vision Science.* 2001. p. 75.
24. Reutebuch SE, Mcgaughey RJ, Andersen H, Carson WW. Accuracy of a high-resolution lidar terrain model under a conifer forest canopy. *2003;29(5):527–35.*
25. Ojuka D, Dindi K, Awori M. Prevalence of Esophageal Adenocarcinoma. *Ann African Surg.* 2018;14(2):82–5.
26. Dawsey SP, Tonui S, Parker RK, Fitzwater JW, Dawsey SM, White RE, et al. Esophageal cancer in young people: A case series of 109 cases and review of the literature. *PLoS One.* 2010;5(11).
27. Jain S, Dhingra S. Pathology of esophageal cancer and Barrett’s esophagus. *Ann Cardiothorac Surg.* 2017 Mar 1;6(2):99–109.
28. Chen Q, Zhuang H, Liu Y. The association between obesity factor and esophageal cancer. Vol. 3, *Journal of Gastrointestinal Oncology.* Pioneer Bioscience Publishing; 2012. p. 226–31.
29. Long E, Beales ILP. The role of obesity in oesophageal cancer development. Vol. 7, *Therapeutic Advances in Gastroenterology.* SAGE Publications; 2014. p. 247–68.

APPENDICES

Appendix I: Informed Consent (English version)

A. INFORMATION

Introduction: Greeting! My name is Dr. Jackson R. Matondo from Muhimbili University of Health and Allied Sciences. I invite you to participate in a study on risks factors for esophageal cancer in Tanzania 2019. I am conducting this study to help identify risk factors for esophageal cancer among patient who are living along the coastal and highland in Tanzania.

What does your participation mean? If you agree to participate in this study, then I am going to ask you some question that might take you five minutes to identify some esophageal cancer risk that you might have.

What are my benefits and risks by participating? We believe by participating in this study you will provide important information that will help future patients to be identified earlier and hence improve care among esophageal cancer patients. You would have helped humanity and left a legacy in science. If you have never screened for esophageal cancer, this exercise will increase your awareness and hence develop health seeking behavior. I do foresee any risk by you taking part in this study.

Confidentiality: The information that you will provide during the study will be kept confidential. Only the researcher will have access to the questionnaires. Your identity will not appear anywhere.

Right to withdrawal: Your participation in this study is voluntary. You have the right to get out of the study anytime if you change your mind even after you have signed the consent form. You won't lose your health or social right to which you are entitled even if you decide not to participate.

Time compensation: There is no time compensation however there is tokens of Tshs. 2000/= for each participants for transport back home.

Who to contact: In case you have questions about this study, you should contact the following: Dr. Jackson R. Matondo (principal Investigator), department of Surgery, Muhimbili university of Health and Allied Sciences, P.O Box 65001, Dar es Salaam, mobile phone 0717614642

In case of questions about your rights as a participant, you may contact Dr. Bruno Sunguya Chairman of the Senate Research and Publications Committee, Muhimbili University of health and Allied Science, P.O Box 65001, Dar es Salaam, mobile number 0685 217272.

Participants signature..... Date.....

Interviewer signature.....Date.....

Appendix II: Questionnaire (English version)

I. INTERVIEW PARAMETERS

- 1. Questionnaire number
- 2. Date of interview ...day/month/year...../...../.....
- 3. Name of interviewer
- 4. Name of ward.....
- 5. Patient file number (MR no) M/A..... (for cases)
- 6. Histology result +ve -ve
- 7. Histology type.....

II. SOCIODEMOGRAPHIC CHARACTERS

- 1. In which date, month and year, were you born? /..... /.....Age.....
(Years)..... Sex
- 2. What is the highest level of education you attained?
 - a. No formal education
 - b. Primary education
 - c. Secondary education (O-level)
 - d. Advanced secondary education (A-level)/college(certificiate)
 - e. Diploma/Advanced diploma
 - f. University (degree/maturs/PHD etc
- 3. Residence
 - a. Division.....years of stay
 - b. District.....years of stay
 - c. Region.....years of stay
- 4. Someone in the family was diagnosed with esophageal cancer (Yes or No)
- 5. If yes choose
 - a. Father
 - b. Mother
 - c. Grandmother /grandfather
 - d. Other relative.....

- 6. What is your occupation?
 - a. Agriculture /Farming
 - b. Business / Trade
 - c. Housewife
 - d. Civil servant
 - e. Other (Specify).....
- 7. What is your marital status?
 - a. Single
 - b. Married
 - c. Cohabiting
 - d. Widow
 - e. Divorced/Separated
- 8. History of obesity in your life
 - a. Yes
 - b. No

III: HABIT

Active smoking

- 9. Do you smoke/have you ever smoked cigarette in the past?
 - a. Yes
 - b. No
- 10. If YES, how old were you when you started to smoke?
- 11. How many cigarettes do you smoke in a day?

Passive smoking

- 12. Did / does someone smoke inside your living apartment?
 - a. Yes
 - b. No
- 13. How long does/did someone inside your apartment smoke?
 - a. Months
 - b.Years

- 14. How many hours per day do/did you spend in smoke filled apartment?
- 15. Does/did someone smoke at your work place?
 - a. Yes
 - b. No
- 16. How long do you work at smoke filled work place?

Alcohol use

- 17. Do/did you drink alcoholic beverages?
 - a. Yes
 - b. No
- 18. How old were you when you started drinking habitually?
- 19. What type of alcoholic beverages
- 20. Have you ever taken hot drink?
 - a. Yes
 - b. No
- 21. What type of drink
- 22. How many times did you drink per day?
 - a. Once per day
 - b. Twice per day
 - c. More than three times per day

IV; DIATERY HISTORY

- 23. Have you ever consumed a red meat?
 - a. Yes
 - b. No (If Yes , answer question number 24)
- 24. How many times did you consume red meat per day?
 - a. A. Once per day
 - b. Twice per day
 - c. More than three times per day

- 25. Have you ever consumed smoked food
 - a) Yes
 - b) No (If yes, answer question number 28).
- 28. What type of smoked food have eaten.....
- 29. Have you experienced heartburn?
 - a. Yes
 - b. No (if Yes go to question 30)
- 30. How old were you when started experienced heartburn.....
- 31. Have you ever swallowed a corrosive substance?
 - c. Yes
 - d. No (If Yes go to question 26)
- 32. What type of corrosive did you swallow? At years old

DIAGNOSTIC TEST

- 33. Have you ever tested for EC cancer?
 - e. Yes
 - f. No
- 34. What was the result after the test...? (Positive or negative)
- 35. Did you ever suffered other esophageal diseases?
 - g. Yes
 - h. No
- 36. Have you undergone surgical operation on stomach?
 - a. Yes
 - b. No
- 37. Have you ever tested for HIV?
 - a. Yes
 - b. No
- 38. If, Yes, what was the result?
 - a. Negative
 - b. Positive

Appendix III: Informed Consent (Swahili version)

VIHATARISHI VYA KANSA YA KOO KWA WATU WAISHIO UKANDA WA PWANI NA NYANDA ZA JUU TANZANIA

FORM YA IDHINI YA KUSHIRIKI

I. TAARIFA

Utangulizi: Salamu! Kwa majina naitwa Dr. Jackson R. Matondo wa Chuo Kikuu cha Afya na Sayansi shirikishi Muhimbili. Ninakualika kushiriki katika utafiti unaohusu vihatarishi vya saratani ya koo kwa watu waishio ukanda wa pwani na nyanda za juu Tanzania.

Dhumuni: Kutambua vihatarishi vya saratani ya koo kwa watu waishio ukanda wa pwani na nyanda za juu Tanzania.

Ushiriki: Nitakuuliza maswali machache kuhusu ufahamu na ushiriki wako kwenye uchunguzi wa saratani ya koo.

Faida na hatari: kwa hushiriki kwako katika utafiti huu utasaidia upatikanaji wa taarifa muhimu zitakazowezesha watengeneze sera na waandaaji mipango katika kuzuia saratani ya koo nchi nzima. Hakuna hatari yoyote ya kiafya au kiuchumi itaweza kukutokea kwa kushiriki katika utafiti huu.

Usiri: Taarifa utakazotoa katika utafiti huu ni siri. Mtafiti pekee ndiye atakayeweza kuziona taarifa hizi. Hata katika utoaji wa taarifa au uchapishaji wa taarifa za utafiti jina lako halite tajwa sehemu yoyote.

Hakiyakujitoa: Ushiriki wako katika utafiti huu ni hiari. Una haki ya kujitoa wakati wowote ukibadili mawazo hata kama ulisaini fomu ya idhini ya kushiriki. Hautopoteza haki yako yoyote ya kiafya au kijamii hata pale utakapoamua kujitoa kushiriki katika utafiti huu.

Kwa mawasiliano: endapo utakuwa na swali lolote linalohusu utafiti huu, wasiliana na wafuatao: Dr. Jackson R. Matondo (mtafiti mkuu) idara ya Upasuaji: chuo Kikuu cha Afya na sayansi shirikishi Muhimbili S.L.P 65001, Dar es Salaam. Simu 0717614642.

Kwa maswali kuhusu haki zako kama mshiriki, unaweza kuwasiliana na Dr. Joyce Masalu, Mwenyekiti wa kitengo cha utafiti, chuo cha Afya na Sayansi shirikishi Muhimbili P.O. Box 65001, Dar es Salaam. Sim: 2150302-6.

II. IDHINI YA KUSHIRIKI

Nimesoma (nimesomewa) taarifa hii kama ilivyoelezwa hapo juu. Nimeuliza (endapo ukipata nafasi ya kuuliza maswali na nimejibiwa. Nimeelewa dhumuni lautafiti huu. Nimeelewa faida, athari na haki yangu ya kujitoa katika utafiti wakati wowote. Ninakubali kwa hiari yangu kushiriki katika utafiti huu.

Sahihyamshiriki.....Tarehe

SahihyamtafitiTarehe

Appendix IV: Questionnaire (Swahili Version)

I. TAARIFA ZA MTAFTITI

1. Namba ya dodoso
2. Tarehe ya
mahojiano.....Tarehe/mwenzi/mwaka...../...../.....
3. Jina la mtafiti.....
4. Jina la wodi.....
5. Namba ya mgonjwa (Mr no) M/A
6. Majina ya kipimo (a) Kansa (b) Hana kansa (aina ya kansa.....)
7. Aina ya Kansa

II. TAARIFA ZA MSHIRIKI

8. Ulizaliwa tarehe ngapi? (siku, mwezi na mwaka) Umri
(miaka).....
9. Unakiwango gani cha elimu?
 - A. Sikuwahi kwenda shule
 - B. Elimu ya msingi
 - C. Elimu ya secondary (kidato cha nne)
 - D. Elimu ya sekondari (kidato cha sita)/chuo ngazi ya cheti
 - E. Chuo ngazi ya Stashahada
 - F. Chuo kikuu (Shahada/uzamili/uzamivu)
10. Unaishi wapi?
 - A. Tarafa.....miaka uliokaa
 - B. Wilaya.....miaka uliokaa
 - C. Mkoa.....miaka uliokaa
11. Kuna ndugu yako amewahi kuwa na kansa ya koo? (Ndio au Hapana)
.....

12. Kama ndio chagua
- A. Baba
 - B. Mama
 - C. Bibi / Babu
 - D. Ndugu mwingine (taja)
13. Unajishughulisha na nini?
- A. Kilimo
 - B. Biashara
 - C. Mama wa nyumbani
 - D. Mwajiriwa
 - E. Nyinginezo (taja)
14. Hali ya ndoa
- A. Sijaolewa
 - B. Nimeolewa
 - C. Ninaishi na mwanaume ila hatujafunga ndoa
 - D. Mjane
 - E. Tumeachana/Tumetengana
15. Unahistoria ya kuwa mnene katika maisha yako?
- A. Ndiyo
 - B. Hapana
16. Umewahi kupima virus vya UKIMWI?
- A. Ndiyo
 - B. Hapana
17. Kama ndiyo, majibu yalikuwaje?
- A. Nina virusi vya UKIMWI
 - B. Sina virusi vya UKIMWI
18. Je umewahi/unavuta sigara?
- A. Ndiyo
 - B. Hapana

19. Kama ndiyo, ulikuwa na umri wa miaka mingapi ulipoanza kuvuta?
..... (miaka)
20. Ulikuwa/unavuta sigara ngapi kwa siku?.....
21. Umewahi kuishi na mtu anayevuta sigara ndani ya nyumba moja?
A. Ndiyo
B. Hapana
22. Kama ndiyo, kwa muda gani?
A. Miezi
- B. Miaka
23. Ulikuwa/unakaa muda gani ndani ya nyumba yenye moshi?
.....(masaa/siku)
24. Kuna mtu anavuta sigara kazini kwako?
A. Ndiyo
B. Hapana
25. Unafanya kazi katika mazingira ya moshi wasigara kwa muda gani kwa siku?.....Miaka?.....
26. Unahistoria ya kunywa pombe?
A. Ndiyo
B. Hapana
27. Ulianza kunywa pombe na miaka mingapi?
28. Aina gani ya pombe ulitumia
29. Ulishawahi kunywa kimwaji cha moto
a. Ndio
b. Hapana
30. Aina gani ya kinywaji
31. Ulikuwa unakunywa hicho kinywaji mara ngapi?
a. Mara moja kwa siku
b. Mara mbili kwa siku
c. Zaidi ya mara tatu kwa siku

32. Ulishawahi kumeza kemikali?
- a. Ndio
 - b. Hapana (kama ndio nenda swali la 26)
33. Je ni aina gani ya kemikali uliyomeza? mwaka uliyomeza
34. Ulishawahi kusikia kiungulia?
- a. Ndio
 - b. Hapana(kama Ndio nenda swali la 28)
35. Je ulikuwa na miaka mingapi uliposikia kiungulia? mwaka
36. Ulishawahi kupimwa saratani ya koo?
- a. Ndio
 - b. Hapana
 - c. Majibu ya kipimo
37. Ulishawahi kuugua magonjwa mengine ya koo
- a.Ndio
 - b.Hapana
38. Ulishawahi kufanyiwa upasuaji kwenye tumbo?
- a. Ndio
 - b. Hapana
39. Ulishawahi kula nyama nyekundu?
- a. Ndio
 - b. Hapana (Kama Ndio jibu swali la 34)
40. Ulishawahi kutumia nyama nyekundu mara ngapi kwa siku?
- a. Mara moja kwa siku
 - b. Mara mbili kwa siku
 - c. Zaidi ya mara moja kwa siku