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Epidemiology and Biostatistics Division

Title: Effects of smoking and alcohol use on oesophageal cancer amongst Black South Africans in Johannesburg from 1999 – 2009

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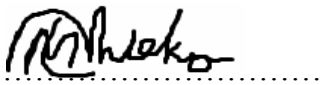
DECLARATION

I, Mandlakayise Lucky Nhleko (student number: 908024) am submitting my research report in partial fulfilment of the requirements of Master of Science in Epidemiology and Biostatistics at the University of the Witwatersrand, School of Public Health. I declare that all materials presented in this report are my work and have not been submitted before for any degree at any other University. Where I used materials/thoughts from other sources, I have duly acknowledged through the conventional referencing.



October 2017

Signature Date

DEDICATION

I wish to dedicate this work to the Nhleko and Simelane family special mentioned is Mrs ZG Nhleko (my mother), Mr MC Nhleko (my father), and Mr ML Simelane (my uncle). The words of encouragement that you used to tell me did not go unheard.

ABSTRACT

Background: Oesophageal cancer is the fourth most common cancer in black South African males with an age-standardised incidence rate of 7.31 per 100 000 in 2010, and sixth in black South African females, 3.59 per 100 000. The adoption of lifestyle behaviours such as tobacco and alcohol use was on the rise in that decade, amongst black South Africans living in Johannesburg.

Aim: The overall aim was to investigate the association of smoking and alcohol use on oesophageal cancer amongst 18 to 74-year-old black South Africans in Johannesburg from 1999 to 2009.

Methods: Secondary analysis were done based on a matched case-control study design. We used the conditional univariate and matched multiple logistic regression for statistical analysis as the main analysis. Gender was ascertained as an effect modifier therefore the analysis were done separately for males and females. Sensitivity analysis of the findings were tested using the unconditional univariate and unmatched multiple logistic regression.

Results: Heavy smokers had an increased likelihood of oesophageal cancer as shown in the conditional multivariate logistic regression (AOR = 9.0; 95% CI: 5.2 – 15.5) in males and (AOR = 5.2; 95% CI: 1.3 – 20.1) in females. Alcohol consumption was a much stronger risk factor for oesophageal cancer among female heavy drinkers (AOR = 2.1; 95% CI: 1.5 – 2.9) relative to the light drinkers, controlling for other variables. There was a significant interaction of tobacco use and alcohol drinking as they acted synergistically to increase the likelihood of oesophageal cancer among current heavy smokers and heavy drinkers, (AOR = 15.0; 95% 7.2 – 31.3) in males and (AOR = 2.7; 95% 0.6 – 11.2) in females, compared to non-drinkers.

Conclusion: We established that over the ten-year study period, smoking and alcohol use were both associated with oesophageal cancer independently and as combined exposures. An increase in sin tax on cigarettes and alcohol as well as increased education on the risk factors associated with the development of oesophageal cancer could be used as interventions to decrease the burden of this disease.

Keywords: **Smoking, Alcohol, Cancer, South Africa**

PREFACE

This research report is submitted to the University of the Witwatersrand, Faculty of Heath Sciences, in partial fulfilment of the requirements for the degree of Master of Science in Epidemiology and Biostatistics. This work has been performed at the Wits School of Public Health (Wits SPH) and National Cancer Registry of South Africa (NCR-SA) under the supervision of Prof Eustasius Musenge (main supervisor) and Dr Chantal Babb de Villiers (co-supervisor). Financial assistance was received from a masters scholarship awarded by the University of the Witwatersrand's School of Public Health with the support from the Atlantic Philanthropies (Wits SPHAP), National Research Fund (NRF), and Health and Welfare Sector Education and Training Authority (HWSETA). I am thankful for the masters scholarship that was awarded.

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Without God, this work could have not been a success, and I thank God for being with me from the preliminary to the concluding level of this work.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

GLOSSARY OF TERMS

1. ***Cancer:*** a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body.
2. ***Demographic characteristics:*** a statistical data about the characteristics of a population, such as the age, gender and income of the people within the population.
3. ***Enzymes:*** can be defined as biological catalysts that increase the rate of chemical reactions without being used up.
4. ***Oesophagal diverticula:*** a pouch that protrudes outward in a weak portion of the oesophageal lining. This pocket-like structure can appear anywhere in the oesophagal lining between the throat and stomach.
5. ***Aetiogenesis:*** a case of an illness or rate of occurrence of a disease or its causal origin.
6. ***Gastroesophageal reflux disease (GERD):*** a digestive disorder that affects the lower oesophagal sphincter, the ring of muscle between the oesophagus and stomach.
7. ***Hiatus Hernia:*** a protrusion of an organ, typically the stomach, through the oesophageal opening in the diaphragm.
8. ***Hydrogen Potassium ATPase (H+ K+ ATPase):*** an enzyme which its purpose is to acidify the stomach.
9. ***Lifestyle factors:*** the modifiable habits and ways of life that can greatly influence overall health and well-being.
10. ***Medical conditions:*** diseases, illnesses or injuries; any physiologic, mental or psychological conditions or disorders.
11. ***National Cancer Registry of South Africa (NCR-SA):*** South Africa's main cancer statistics source, it collates and analyses cancer cases diagnosed in pathology

laboratories (both public and private) nationwide and reports annual cancer incidence rates.

12. ***Oesophageal cancer:*** this type of cancer starts in the mucosa and grows through the submucosa and the muscle layer of the oesophagus. There are two main types of oesophageal cancer namely the OSCC and ADC. OSCC is frequently lined with squamous cells and it can occur anywhere along the oesophagus. ADCs are not typically part of the inner lining of the oesophagus and the gland cells replace an area of squamous cells in Barrett's oesophagus prior the development of ADC.

13. ***Proton pump inhibitors (PPIs):*** a group of drugs that reduce the secretion of gastric (stomach) acid.
14. ***Statistics South Africa (Stats SA):*** the national statistical service of South Africa, with the goal of producing timely, accurate, and official statistics to advance economic growth, development, and democracy.
15. ***Surveillance, Epidemiology, and End Results Program (SEER):*** a source of epidemiologic information on the incidence and survival rates of cancer in the United States.

LIST OF ABBREVIATIONS

General abbreviations

ADC	Adenocarcinoma
AOR	Adjusted Odds Ratio
AUC of the ROC	Area Under Curve of the Receiver Operating Characteristic
CDC	Centers for Disease Prevention and Control
CERG	Cancer Epidemiology Research Group
CI	Confidence Interval
Cs	Number of cases
DAG	Directed Acyclic Graph
DNA	Deoxyribonucleic Acid
DUA	Data Use Agreement
EDTA	Ethylenediamine Tetraacetic Acid
ELISA	Enzyme-Linked Immunosorbent Assay
GERD	Gastroesophageal Reflux Disease
H+ K+ ATPase	Hydrogen Potassium ATPase
HBP	High Blood Pressure
HIV	Human Immunodeficiency Virus
IARC	International Agency for Research of Cancer
ICD	International Classification of Diseases
JCS	Johannesburg Cancer Study
JCCCS	Johannesburg Cancer Case-Control Study
ml	Millilitre
NCR-SA	National Cancer Registry of South Africa
NICD	National Institute for Communicable Diseases
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OSCC	Oesophageal Squamous Cell Cancer
PPIs	Proton Pump Inhibitors
SASCO	South African Standard Classification of Occupations

SD	Standard Deviation
SEER	Surveillance, Epidemiology, and End Results Program
Stats SA	Statistics South Africa
STIs	Sexually Transmitted Infections
UOR	Unadjusted Odds Ratio

Symbols used

=	Equality
>	Greater than
<	Less than
≥	Greater than or equal to
≤	Less than or equal to
/	Division slash
·	Decimal point, decimal separator

CHAPTER 1

INTRODUCTION

This chapter covers the introduction including the background of oesophageal cancer, symptoms, the burden in South Africa, risk factors, modification of lifestyle behaviours by black South Africans and highlights the research question. This section also covers the statement of problem, justification of the study, aims and objectives and ends with literature review.

1.1. Background

The oesophagus carries the useful and toxic substances into the stomach of humans, and like many other parts of the body, the oesophagus is susceptible to cancer (1). There are two main types of oesophageal cancer namely oesophageal squamous cell cancer (OSCC) and adenocarcinoma (ADC) (1). The common symptoms of oesophageal cancer include problems in eating, swallowing, weight loss, hoarse voice and a sore throat (2). Many patients do not develop any obvious symptoms of oesophageal cancer until the cancer is advanced (3). Early detection of oesophageal cancer is critical for treatment and long-term survival of patients.

OSCC is the most common type of oesophageal cancer in developing countries, including South Africa. There is about 80% of oesophageal cancer cases occurring in the developing countries in which nearly all the cases are OSCC (4). However, the ADC cases have increased in the most developed countries, although OSCC still predominates in some of the countries (5, 6). Oesophageal cancer is the eighth leading cancer worldwide, with an estimated 456 000 cases in 2012 (3.2% of the total cancers) and sixth most common cause of mortality from cancer with an estimated 400 000 deaths (4.9% of the total cancers) (7). Oesophageal cancer is the fourth most common cancer in black South African males with the Age-Standardised Incidence Rate (ASIR) of 7.31 per 100 000 in 2010 (8). Oesophageal cancer is the sixth in black South African females with the ASIR of 3.59 per 100 000 in 2010 (8). These figures include both ADC and OSCC sub-types (8).

It has been noted that the migrants will leave their respective places of residence due to many pulling and pushing factors (9) and Johannesburg and the Gauteng province at large have become a zone of attraction. The population size of Gauteng province reached 12.91 million in 2014 (10). The population of Gauteng province was composed of mainly black Africans (77.4%) in 2011 (11). People modify their lifestyles as they move from their places of origin to Johannesburg and adapt to urbanisation such as using tobacco and alcohol (12-14). Therefore, the question this study is answering is what is the association of smoking and alcohol use on oesophageal cancer amongst black South Africans in Johannesburg? This research report presents a detailed analysis of the association of tobacco use and alcohol drinking on oesophageal cancer amongst 18 to 74-year-old black South Africans in Johannesburg from 1999 to 2009.

1.2. Statement of problem

Over the last decade, black Africans have increased their usage of tobacco and alcohol (9, 70-73). A study done in 2013 projected that the increased number of adult smokers in Africa is anticipated and the number will increase from 77 million to 572 million by 2100 (74). Researchers have estimated that Africa alone could account for 26% of the world's smokers by 2100 if the smoking problem is not addressed on time (74). Such high numbers indicate the need to apply intervention measures to combat tobacco use amongst African smokers.

Consumption of commercial alcoholic drinks has increased while reducing the consumption of traditional beverages (13). The adoption of lifestyle behaviours such as smoking and alcohol consumption has risen in Johannesburg (9). As mentioned earlier, these lifestyle behaviours are associated with urbanisation and economic development (75). Smoking and alcohol use are primary exposures for oesophageal cancer and other forms of cancer (76, 43, 77, 25). Such modification of lifestyle behaviours could lead to the increased risk of oesophageal cancer as urbanisation has taken place.

1.3. Justification of the study

The incidence of oesophageal cancer has increased in South Africa since the 1960s (9, 13). Some studies reported an association between smoking and alcohol use on oesophageal cancer amongst different population groups including black South Africans (15-25). People change their lifestyles as they migrate to Johannesburg, including the use of tobacco and alcohol (12-14). Smoking and alcohol intake is associated with oesophageal cancer as both independently and combined exposures (13, 26). Studies done in the Eastern Cape, South Africa reported a high incidence rate of oesophageal cancer (9, 27-29). The high incidence rate of oesophageal cancer in Eastern Cape was associated with other risk factors such as poor nutritional status and contaminated maize (9, 27-29).

Understanding the association of smoking and alcohol use on oesophageal cancer can provide valuable information on how this cancer can be prevented in South Africa. The association of tobacco and alcohol use with oesophageal cancer in an African population has not been well investigated with quite large dataset. It is not well known to what degree smoking and alcohol intake are contributing to oesophageal cancer in black South Africans or other developing countries. This study analysed secondary data to assess the association of smoking and alcohol use on oesophageal cancer in black South Africans. Few studies have been done in South Africa or other African countries investigating the association of tobacco use and alcohol consumption on oesophageal cancer using quite large dataset. The majority of the studies in this field have been done in developed nations.

1.4. Aim and specific objectives

1.4.1. Overall Aim:

To investigate the association of smoking and alcohol consumption on oesophageal cancer amongst 18 to 74-year-old black South Africans from 1999 to 2009 in the Johannesburg Cancer Case-control Study (JCS).

1.4.2. Objectives

1. To describe the characteristics of oesophageal cancer amongst 18 to 74-year-old black South Africans from 1999 to 2009 in the JCS, stratified by sex.

2. To determine the association of smoking and alcohol consumption on oesophageal cancer amongst 18 to 74-year-old black South Africans from 1999 to 2009 in the JCS, stratified by sex.

1.5. Literature review

1.5.1. Pathogenesis of oesophageal cancer

Oesophageal cancers are mainly either OSCC or ADC (1). Other carcinomas such as melanomas, leiomyosarcomas, carcinoids, and lymphomas may develop in the oesophagus although they are rare (3). Most of the ADCs are found in the distal oesophageal whereas OSCC is more evenly distributed between the middle and lower third (1, 141, 30-32).

Oesophageal cancer is known to be a disease of the elderly. The pathogenesis of oesophageal cancer is still not well known (3). Data from animal experiments suggest that oxidative damage from factors such as smoking increase the cell turnover which is highly likely to initiate the carcinogenic process (34). Once cancer develops, it may spread at the higher rate. There is about 14 to 21% of submucosal cancers (T1 lesions), and 38 to 60% of cancers that invade muscle (T2 lesions) thought to be associated with spread to lymph nodes (32, 35). During the diagnosis of oesophageal cancer, more than 50% of patients have either unresectable tumours or have radiographically visible metastases (3). Patients often do not get diagnosed until the oesophageal

cancer is symptomatic and at an advanced stage which is why most are unresectable. The 5-year survival for oesophageal cancer depends on the stage at which this cancer is being diagnosed (36). The 5-year survival for localised is (37.8%), regional (19.8%), distant (3.4%) and unstaged (10.5%) oesophageal cancer in all population groups and sexes (36).

1.5.2. Smoking and oesophageal cancer

Some studies suggest that smoking is associated with OSCC and ADC (37, 38). Tobacco use is thought to introduce tobacco carcinogens particularly nitrosamines upon smoking (39). Studies have shown that there is a positive linear relationship between the oesophageal cancer with the amount of tobacco intake per day as well as the duration of smoking (37-40).

1.5.3. Alcohol use and oesophageal cancer

Drinking alcohol increases the risk of developing oesophageal cancer (41-44). The possibilities of getting oesophageal cancer increases with increased alcohol use (45-48). Alcohol consumption is associated with the increased risk of developing OSCC type more than ADC (46-49). Upon drinking, the DNA in cells lining the inside of the oesophagus are damaged with oesophageal cancer being one of the possible outcomes (36). By definition, cancers are caused by DNA damage that can turn on oncogenes or turn off tumour suppressor genes. The DNA of oesophageal cancer cells often shows changes in many different genes (36). However, it is still not clear if there are specific gene changes that can be found in all or most oesophageal cancers.

1.5.4. Interaction of smoking and alcohol use and oesophageal cancer

Factors that cause chronic irritation and inflammation of the oesophageal mucosa could potentially cause OSCCs (3). Alcohol consumption is one of the top factors that cause OSCC (3). The combination of smoking and alcohol use leads to the greater possibility to develop OSCC notably but not ADC (37, 38, 50, 51). The combination of smoking and alcohol use also increases the risk of head and neck cancer (3, 52). This association enables the clinicians to identify

clinically unsuspected OSCC; hence this identification of unsuspected OSCC was achieved in 1 to 2% of patients with head and neck cancers in developed countries (3, 52).

The lifetime risk of oesophageal cancer is higher in men as compared to women (53, 8). In black South Africans, males smoke more than females. A study done in black South Africans found that 19.1% of men and 2.1% of women were smokers (54). There is also the higher prevalence of alcohol consumption in males than females. Researchers revealed that there were 15.2% black South Africans men and 2.1% black South African women who were drinkers (54). The differences in smoking and drinking habits according to sex leads to different risks of oesophageal cancer across the sexes (54). Avoidance of tobacco and alcohol use is one of the best ways of limiting the oesophageal cancer (45). However, we do not know to what degree smoking and alcohol use are contributing to oesophageal cancer in black South Africans.

1.5.5. Other risk factors and oesophageal cancer

Other than smoking and alcohol consumption there are other risk factors associated with oesophageal cancer (27-29). The risk for oesophageal cancer increases with age with a mean age at diagnosis of 67 years (33, 1). Low socioeconomic status is associated with the increased risk of developing OSCC but not ADC (38, 55, 56). There is a link between obesity and ADC especially in westernised countries (37, 57, 58, 44). Grass thatched houses promote the inhabitation of fungi and bacteria which could be a risk for oesophageal cancer (59). In the Eastern Cape, South Africa there was a high incidence rate of oesophageal cancer that was suspected to be associated with poor nutritional status and Fusarium species contaminated maize (9, 27-29). Oesophageal cancer cases are decreasing in developed countries due to the improvement of their nutritional status (60). During the decomposition of food by achalasia and oesophagal diverticula, various irritant chemicals are released which can result in oesophageal cancer (61, 62). Consumption of extremely hot beverages also increases the incidence of OSCC (63-65). A study done in Marsabit in Northern Kenya on the analysis of water contaminated with toxic chemicals such as nitrates,

nitrites and arsenic are associated with the increased risk of oesophageal cancer (66). Some people have an increased risk of developing certain cancers due to hereditary traits from their parents. However, oesophageal cancer does not seem to be linked in families and inherited gene mutations are not thought to be a major cause of this disease (67, 68) but still needs further investigation.

1.5.6. Global, regional, national (South Africa) statistics and oesophageal cancer

There is limited research on oesophageal cancer being done worldwide. However, the important epidemiologic patterns of oesophageal cancer have been taking place worldwide. The oesophageal cancer is important to both developed and developing countries because of the high mortality rate from this cancer. Oesophageal cancer is the eighth leading cancer worldwide, with an estimated 456 000 cases in 2012 (3.2% of the total cancers) and sixth most common cause of mortality from cancer with an estimated 400 000 deaths (4.9% of the total cancers) (7). These figures include all sub-types including the more typical ADC and OSCC. Around 80% of the cases worldwide occur in less developed regions, especially in Africa (7).

Oesophageal cancer incidence rates worldwide in men are more than double in women (male: female ratio 2.4:1) (7, 69, 8). In both men and women there are more than 20-fold differences in incidence between the different regions of the world, with rates ranging from 0.8 per 100 000 in Western Africa to 17.8 per 100 000 in Eastern Asia in men, and 0.2 per 100 000 in Micronesia/Polynesia to 7.8 per 100 000 in Eastern Africa in women (7). The lifetime risk of developing oesophageal cancer is 1:111 in black South African males and 1:232 in black South African females (8). Oesophageal cancer was the second most common cancer in black South African males with an ASIR of 14.1 per 100 000 in 1999 and third in black South African females with an ASIR of 7.0 per 100 000 (144). As mentioned earlier this is believed to relate to the differences amounting to drinking and smoking between the sexes.

Oesophageal cancer has a very poor survival (overall ratio of mortality to the incidence of 0.88) (7). The oesophageal cancer mortality closely follows the geographical patterns of incidence with

the highest mortality rates occurring in Eastern Asia (14.1 per 100 000) and Southern Africa (12.8 per 100 000) in men and in Eastern Africa (7.3 per 100 000) and Southern Africa (6.2 per 100 000) in women (7).

1.5.7. Construction of DAG

In this study, the relevant conditioning variables were identified not only by analysing the secondary data but by examining the literature. The DAG was used to investigate further the effects on oesophageal cancer of the primary exposure of interest which is the lifestyle (81). According to the literature review, the development of oesophageal cancer is the consequence of a multifactorial process. However, only the variables available in the secondary data were used to construct DAG in this study after analysing the literature. These multiple factors were grouped into four well known and suspected important risk factors for oesophageal cancer namely, demographic characteristics, socioeconomic status, medical condition, and lifestyle. Demographic characteristics included place of birth, marital status, sex, and age. Socioeconomic status component included housing material, domestic fuel, education, and occupation. A medical condition included Human Immunodeficiency Virus (HIV). Lifestyle component included smoking, alcohol use, the interaction of smoking and alcohol use, and snuff.

1.5.8. Assumptions for DAG

Assumptions for DAG shown in Figure 1 were made by analysing the relevant reports and articles from the literature which are in agreement with Bradford Hill's criteria (82). The assumptions are as follows:

1. Lifestyle directly affects oesophageal cancer.
2. Lifestyle causes oesophageal cancer through medical condition.
3. Lifestyle is directly affected by demographic characteristics, and also the demographic. characteristics directly affect oesophageal cancer.
4. Lifestyle is directly affected by the socioeconomic status, and also the socioeconomic status directly affects oesophageal cancer.

1.5.9. Causal directed acyclic graph (causal DAG)

Direct and indirect causal or non-causal paths were identified. There was one direct causal path with a directed edge leading from lifestyle to oesophageal cancer which is a causal hypothesis of interest and was not considered as a backdoor path (Path no 1). Furthermore, there was one pathway identified starting with a directed edge from lifestyle and passing through one node to oesophageal cancer. It represented indirect paths via mediator which was a medical condition, and it was also not considered as a backdoor path (Path no 2). There were eight opened backdoor non-causal paths (Path no 3, 4, 5, 6, 7, 8, 9, and 10). They were two closed backdoor non-causal paths (Path no 11 and 12) (Figure 1 and Table 1).

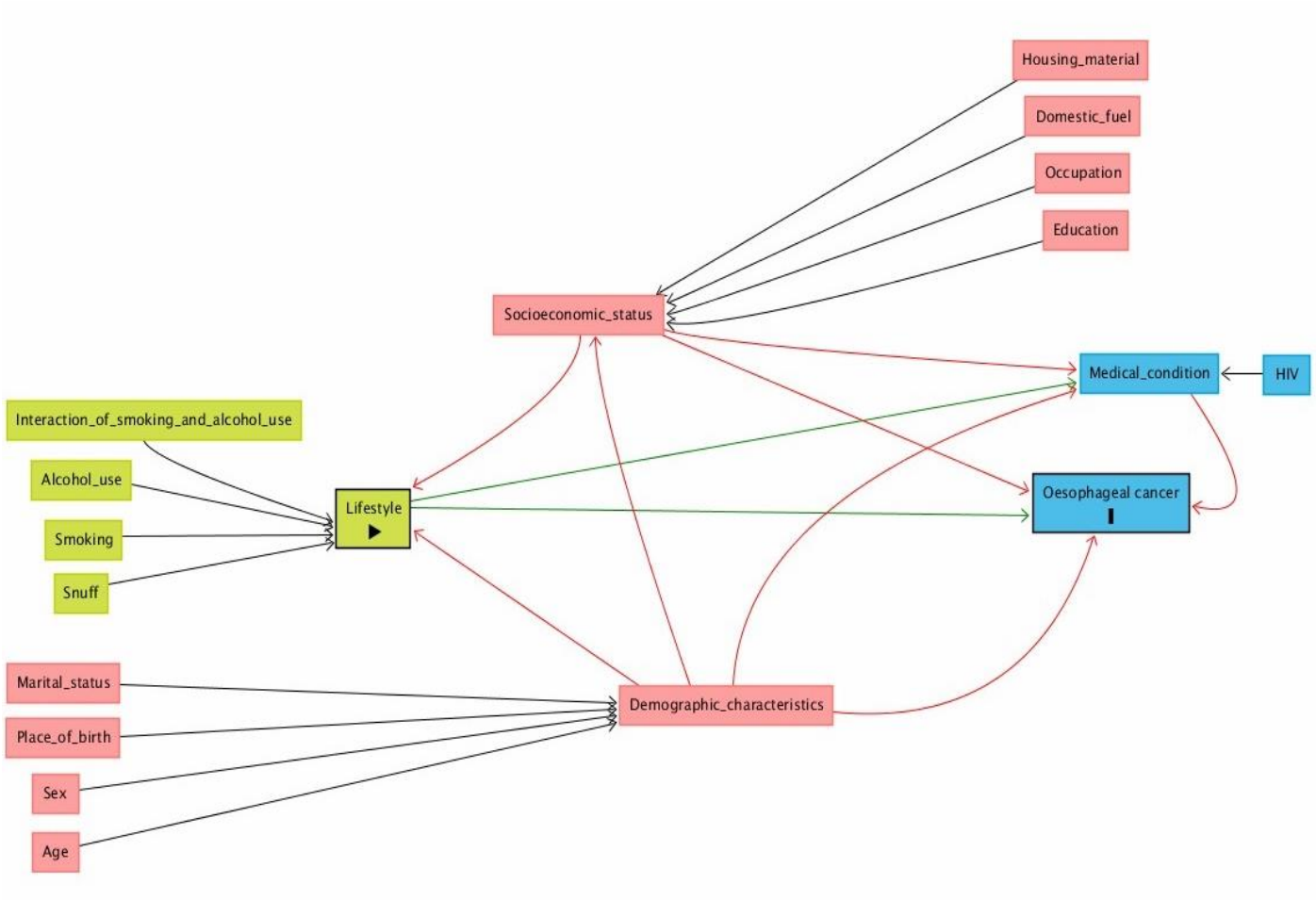

Figure 1: A directed acyclic graph is depicting the relationship between potentially important variables in the association of lifestyle and oesophageal cancer

Table 1: Causal and non-causal pathways showing the relationship between potentially important variables in the association of lifestyle and oesophageal cancer

	Lists of causal and non-causal pathways		
No	**Path**	**Type**	**State**
1	Lifestyle → Oesophageal cancer	Causal	Opened
2	Lifestyle → Medical condition → Oesophageal cancer	Causal	Opened
3	Lifestyle ← Demographic characteristics → Oesophageal cancer	Non-causal	Opened
4	Lifestyle ← Socioeconomic status → Oesophageal cancer	Non-causal	Opened
5	Lifestyle ← Demographic characteristics ← Socioeconomic status → Oesophageal cancer	Non-causal	Opened
6	Lifestyle ← Socioeconomic status ← Demographic characteristics → Oesophageal cancer	Non-causal	Opened
7	Lifestyle ← Demographic characteristics → Medical condition → Oesophageal cancer	Non-causal	Opened
8	Lifestyle ← Socioeconomic status → Medical condition → Oesophageal cancer	Non-causal	Opened
9	Lifestyle ← Demographic characteristics → Socioeconomic status → Medical condition → Oesophageal cancer	Non-causal	Opened
10	Lifestyle ← Socioeconomic status ← Demographic characteristics → Medical condition → Oesophageal cancer	Non-causal	Opened
11	Lifestyle ← Demographic characteristics → Medical condition ← Socioeconomic status → Oesophageal cancer	Non-causal	Closed
12	Lifestyle ← Socioeconomic status → Medical condition ← Demographic characteristics → Oesophageal cancer	Non-causal	Closed

1.5.10. Causal paths

Smoking and alcohol use can directly cause oesophageal cancer without mediators. Upon alcohol consumption, the DNA in cells that line the inside of the oesophagus are damaged, with oesophageal cancer being one of the possible outcomes. Furthermore, there was one pathway identified starting with a directed edge from lifestyle and passing through one node to oesophageal cancer. It represents indirect paths via mediator which is the medical condition, and it is also not a backdoor path (Path no 2). Smoking and drinking can lead to obesity. There is a link between obesity and the risk of ADC development which is one of the types of oesophageal cancer. Several studies have linked obesity with ADC (87-89).

Drinkers have been shown to develop GERD (90). Protein pump inhibitors (PPIs) are used to treat GERD by reducing the production of gastric acid that is thought to be necessary for the formation of most cancers in the oesophagus. PPIs block the enzyme (H+ K+ ATPase) in the wall of the stomach that produces gastric acid. Sometimes the patient may not respond to PPIs, and then GERD is untreated and, finally, the ADC oesophageal cancer is a possible outcome (91). Furthermore, combined Non-steroidal anti-Inflammatory drugs (NSAIDs) and PPIs therapy can be used to treat GERD (92).

1.5.11. Non-causal paths

This study shows that they were eight backdoor non-causal routes and their states were open (Path no 3, 4, 5, 6, 7, 8, 9 and 10). The fact that these routes are unconditionally opened, non-causal, and have no colliders suggest that they are confounding paths. However, conditioning non-colliders on these eight backdoor non-causal routes caused the association between lifestyle and oesophageal cancer. The state of the paths became closed afterwards. For instance, in route no 4 where socioeconomic status directly affects lifestyle and then the socioeconomic status leads to the development of oesophageal cancer. The possible explanation for such a relationship in path no 4 is that the patients do not have to be a smoker for them to develop oesophageal cancer.

Patients may also get exposure to smoke through their socioeconomic status such as exposure to potentially noxious smoke while working. The smoky domestic fuel used for cooking and heating could also contribute in this cycle.

In path no 4, (Lifestyle ← [Socioeconomic status] → Oesophageal cancer) blockage of socioeconomic status leads to an association between lifestyle and oesophageal cancer thus the state of the path shifted from open to close. This study also adjusted the socioeconomic status even during the regression models.

This study found two backdoor non-causal ways and their states are close (Path no 11 and 12). These non-causal pathways are classified as close because they included colliders (a node that is a common effect of at least two other nodes on that path). The collider in this present study is the medical condition. In route, no 11 and 12, the two risk factors namely socioeconomic status and demographic characteristics caused the medical condition. The occupation of the patient which is a socioeconomic variable can determine the exposure status to potentially noxious. Regarding the place of birth which is a demographic variable, there is an increased risk of developing oesophageal cancer among patients with the rural background as they migrated to urban areas for better opportunities such as the job. There is more possibility for them to be exposed to potentially noxious smoke while working depending on the type of occupation. This study did not condition on colliders paths no 11 and 12. For instance, this study did not adjust for HIV which is the medical variable even in the regression models. Conditioning on colliders may open the paths at those nodes to create an artificial association. Therefore, the collider-stratification bias was avoided in this present study (93).

1.5.12. Minimum sufficient sets

The minimum sufficient sets for blockage were [Demographic characteristics, Socioeconomic status]. If the backdoor paths between lifestyle which is the exposure of interest (smoking, alcohol use, the interaction of smoking and alcohol use, and snuff) and oesophageal cancer which is the

outcome of interest) remain open. Then the association detected between lifestyle and oesophageal cancer could be affected by mixed effects or potential confounders or by effect modifiers. These backdoor paths may not reflect the actual relationship or real magnitude of the association between these variables. However, the blockage of backdoor pathways led to a statistical association between lifestyle and oesophageal cancer. It reflected a real association that may be causal or non-causal between the lifestyle and oesophageal cancer afterwards. The Bradford Hill's criteria were used to establish whether the existing association is causal or not.

The key message here is that oesophageal cancer has multiple risk factors or contributing causes. Some of these risk factors are common to more than one disease especially non-communicable diseases considering that oesophageal cancer is also a non-communicable disease. Many associations exist between these risk factors namely demographic characteristics, socioeconomic status, lifestyle, and medical conditions. The strategy in this study was to identify as many relationships with the primary goal to point out all potential confounders or effect modifiers that would be identified and controlled for in the subsequent statistical (regression) analysis. As such, this study identified many backdoor paths between lifestyle and oesophageal cancer. It also identified the covariates which should be considered as potential confounders and adjusted for in subsequent analysis (e.g., included in regression models). Importantly, the concept of DAGs in this study also excluded the specific covariates from such analysis after identifying them. Inclusion and exclusion of such covariates had to be in agreement with Bradford Hill's criteria as mentioned earlier. These diverse backdoor paths could be blocked using a minimum sufficient set after identifying it. To take into account that controlling a collider in a pathway is the problem because it opens other channels which would require blockage. Therefore, the possible effects of confounders and effect modifiers using logistic regression for stratified analysis by sex were also explored and assessed the statistically significant in this study.

CHAPTER 2

METHODS

2.1. Introduction

This section covers the study design and study population, selection of cases and controls, sample size, description of the primary dataset, risk categories and variables for analysis, data processing methods and data analysis and ends with ethical considerations.

2.2. Study design and study population

Secondary data from the JCS at CERG based at the National Cancer Registry of South Africa (NCR-SA) was analysed. The study designs used in this study were unmatched and matched case-control study. The study population were adult black South African patients who were diagnosed with oesophageal cancer, and smoking and alcohol consumption unrelated cancers at Chris Hani Baragwanath, Hillbrow and Johannesburg hospital located in Johannesburg from 1999 to 2009.

2.3. Selection of cases and controls

Cases were study participants diagnosed with oesophageal cancer. Controls were study participants that had no cancers related to smoking and alcohol use. The use of other cancers is an International Agency for Research of Cancer (IARC) approved research method (76, 43). Each case and control were randomly matched for age, place of birth, and sex using ccmatch to clarify the risk factors for oesophageal cancer (84). The ratio of controls to cases of 1:1 was achieved in this study thus the controls and cases were approximately equal, and there was no possibility of overmatching (85, 86).

2.4. Sample size

The study is a secondary data analysis of data collected for the JCS. This case-control study comprised of a final selection of 5704 study participants of which 839 were oesophageal cancer cases and 4865 controls collected from the period of 1999 to 2009 in the unmatched case-control

study. Out of the 5704 study participants, 1836 were males, and 3868 were females. Of the 1836 men, 28.8% were oesophageal cancer cases and 71.2% controls. Of the 3868 females, 8.0% were oesophageal cancer cases and 92.0% controls (Figure 2 and Figure 3).

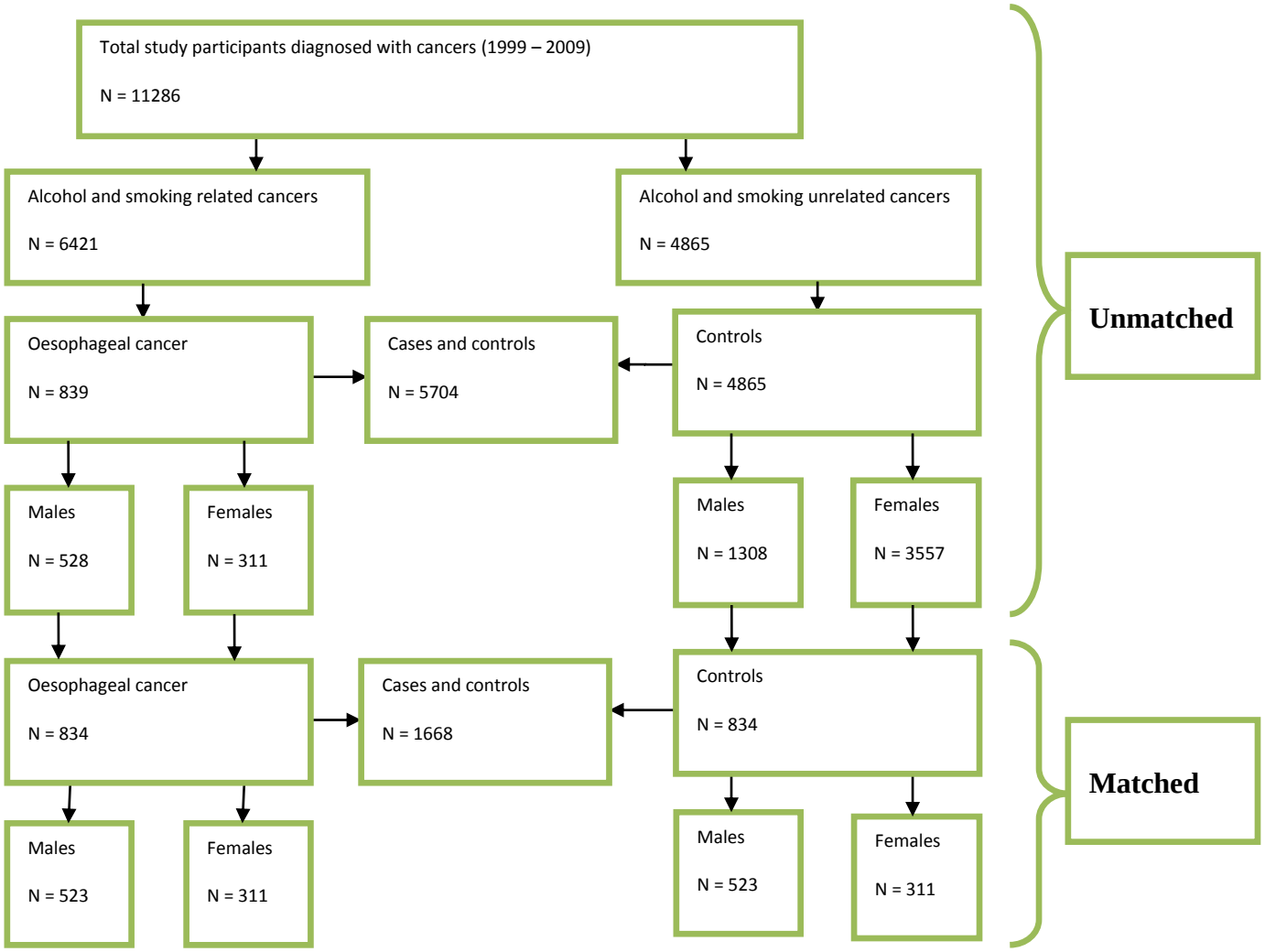

Figure 2: Data flow chart for the unmatched and matched oesophageal cancer case-control studies investigating the association of smoking and alcohol consumption on oesophageal cancer. Key: N (study participants).

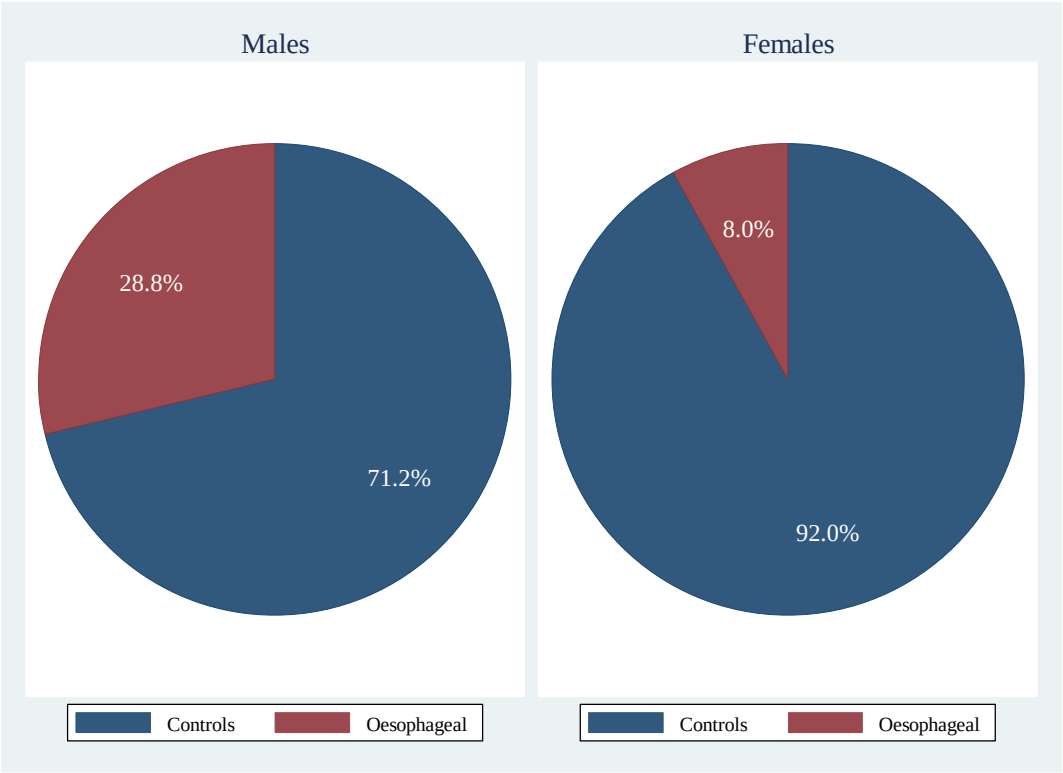

Figure 3: Graphs showing the distribution of oesophageal cancer cases and controls stratified by sex for the unmatched oesophageal cancer case-control data

2.5. Description of the primary data

Nurses trained in interviewing, interviewed adult black South African patients with newly diagnosed cancers including oesophageal cancer, at Chris Hani Baragwanath, Hillbrow and Johannesburg hospital located in Johannesburg using a structured three-page questionnaire (9). The interview was done using the preferred language of the participant (usually in Zulu or Sotho) following written informed consent. The designed questionnaires were anonymous and included questions on age, birthplace, language, education, housing material, occupation, HIV status, type of domestic fuel, snuff usage, and smoking and alcohol consumption. For 90% of the patients, the histology, haematology or cytology was used to confirm the diagnosis.

In addition to the structured questionnaire, interviewers asked all patients aged 55 or less about previous HIV testing from November 2004. Interviewers asked all recruited patients on prior HIV testing after November 2006 (78). Nurse counsellors took blood samples from patients at the time of interview after getting the consent. Blood samples were collected in a 4 millilitre (ml) Ethylenediamine Tetraacetic Acid (EDTA) purple top and a 10 ml red-top plain vacutainers and

then tested for HIV-1 using a single Vironostika (HIV Uniform II plus O) micro Enzyme-Linked Immunosorbent Assay (ELISA) test. All the tests were performed at the Serology Laboratory, Centre for HIV and Sexually Transmitted Infections (STIs), and National Institute for Communicable Diseases (NICD) in Johannesburg (78). The University of the Witwatersrand Medical Research Ethics Committee approved the study (M140271).

2.6. Risk categories and variables for analysis

This present study grouped the risk factors and variables for analysis according to demographic characteristics, socioeconomic status, medical condition and lifestyle (Table 2). South African Standard Classification of Occupations (SASCO) manual was used to classify the study participants according to the type of industry or workplace in which they usually worked (79). The non-noxious category included managerial, administrative, clerical, sales personnel, homemakers, students, and unemployed study participants. The noxious group included metal and non-metallic mineral, chemical, petroleum, coal, rubber, plastics, wood and paper manufacturing and processing, the motor vehicle industry, construction, and mining and quarrying. Electricity is the use of electrical heaters whereas non-electric domestic fuel category included wood, charcoal, coal, anthracite, paraffin, and gas (9).

This research took into account that some study participants who may have given up smoking due to their illness. This present study classified the study participants who stopped smoking more than 5 years prior the date of an interview as former smokers while it classified those who smoked within 5 years of the date as current smokers. The non-smokers were classified as (<1g/day). Current smokers and ex-smokers were then subdivided into light (1-14g/day), and heavy (>=15g/day) current smokers assuming the weight of 1g for commercial cigarettes and a conservative 1g for pipes (25). The frequency of consumption of alcohol from maize, sorghum, other traditional home brewed beers, commercial beer, wine, commercial, and home-distilled spirit, and other alcoholic drinks was classified. Therefore, the non-drinkers were (<1 drink per

week), moderate drinkers (1-7 drinks/week for women, 1-14 drinks/week for men) and heavy drinkers (8 or more drinks/week for women, 15 or more drinks/week for men) (80).

Table 2: Risk categories and variables for analysis

Demographic characteristics	Socioeconomic status	Medical condition	Lifestyle
Age group (Years) 18 – 44 45 – 54 55 – 64 65 – 74	**Education** Tertiary Non-education Primary Secondary	**HIV status** Positive Negative	**Categorised smoking** Non-smokers **Current smokers** Light current smokers Heavy current smokers **Ex-smokers** Light ex-smokers Heavy ex-smokers **Uncategorised smoking** Ever smoked
Place of birth Urban Rural	**Housing material** Brick/concrete Non-brick/ non-concrete Others		**Smoking duration (years)** 1 – 15 16 – 30 31 – 45 46 and more
Language Zulu Xhosa Sotho Tswana Others	**Occupation** Non-noxious Potentially noxious Others		**Age at start smoking (years)** 7 – 15 16 – 20 21 – 25 26 and more
Marital status Single/never married Married/living together Widowed Separated	**Cooking and heating fuel** Electric Non-electric Others		**Years since quitting smoking (years)** 1 – 15 16 – 20 21 – 25
	Indoor and outdoor domestic fuel Electric inside Non-electric inside Non-electric outside Others		**Type of cigarette** Hand rolled Manufactured
			Snuff user Never a snuff user Ever a snuff user
			Categorised alcohol Non-drinkers Moderate drinkers Heavy drinkers **Uncategorised alcohol** Ever drank
			Categorised smoking and alcohol Neither smoked + neither drank Moderate drinkers only Heavy drinkers only Light current smokers only Light current smokers + moderate drinkers Light current smokers + heavy drinkers Heavy current smokers only Heavy current smokers +moderate drinkers Heavy current smokers+ heavy drinkers Light ex-smokers only Light ex-smokers + moderate drinkers Light ex-smokers + heavy drinkers Heavy ex-smokers only Heavy ex-smokers + moderate drinkers Heavy ex-smokers + heavy drinkers **Uncategorised smoking and alcohol** Only drank Only smoked Both smoked and drank

2.7. Data cleaning and quality checks

All data cleaning and analyses were conducted in STATA 13. Tabulation was used in order to check the missing variables. Inconsistencies in the data were checked in terms of misclassification of the type of cancer using International Classification of Diseases (ICD-O-3) as some were not consistent with the definitions of the type of cancers given in the source document (83). Data selection strategy was done through the exclusion of smoking and alcohol use related cancers from the controls. Consequently, the data management part was done through coding or recoding of variables such as education before the data analysis started.

2.8. Statistical analysis

The models were built using unmatched and matched multiple logistic logistic regression in this study. The unmatched multiple logistic logistic regression was used in the unmatched data. The matched multiple logistic regression was employed for inferential statistics in the matched data. Gender was ascertained as an effect modifier therefore the analysis were done separately for males and females. Sensitivity analysis of the findings were tested using the unconditional univariate and unmatched multiple logistic regression.

2.8.1. Descriptive analysis of the unmatched and matched case-control data

The normality of the continuous variables such as age was checked using histograms. All the analyses were stratified by sex, and the oesophageal cancer was the outcome of interest. Continuous variables such as age were summarised using mean and standard deviation and compared using t-test. Categorical variables such as education were summarised using percentages. We used frequency tables to display the percentage distribution of the variables.

2.8.2. Univariate and multivariate logistic regression of the unmatched case-control data

Chi-squared test was employed to assess the association of the categorical variables of interest such as education on oesophageal cancer. Fisher's exact test was also utilised to examine the association of the categorical variables of interest with smaller sample size such as housing

material on oesophageal cancer. The association of smoking and alcohol consumption with oesophageal cancer stratified by sex were investigated both separately and as combined exposures. Unconditional univariate logistic regression was performed for all the variables and checked the statistical significance at the 5% level. Multivariate logistic regression models were then built by adding the exposures that were statistically significant at the 5% level. The measure of smoking and alcohol use on oesophageal cancer were estimated by using adjusted odds ratios (AORs) derived from unconditional, unmatched multiple logistic regression. Multivariate logistic regression was used to control the possible confounders. Specifically, the AORs and 95% confidence intervals (CIs) were calculated from unconditional logistic models adjusted for age group, place of birth, education, housing materials, occupation, the type of domestic fuel, and snuff depending on sex for study participants. The fully adjusted models are presented in Chapter 3. Hosmer-Lemeshow test and Area Under Curve of the Receiver Operating Characteristic (AUC) were used to check the goodness of fit.

2.8.3. Univariate and multivariate logistic regression of the matched case-control data

The McNemar's Chi-squared test was employed to investigate the association of the categorical variables of interest such place of birth on oesophageal cancer. Symmetry test was used to examine the association of the categorical variables of interest on oesophageal cancer where the discrete levels of the exposure were multiple such as education. The association of smoking and alcohol consumption with oesophageal cancer stratified by sex were investigated both separately and as combined exposures. Conditional univariate logistic regression was performed for all the variables except in age group, place of birth and sex. The statistical significance at the 5% level was also checked. Multivariate logistic regression models were then built by adding the exposures that were statistically significant at the 5% level. The measure of smoking and alcohol use on oesophageal cancer were estimated by using adjusted odds ratios (AORs) derived from conditional, matched multiple logistic regression. Conditional multivariate logistic regression was used to control the possible confounders. Specifically, the AORs and 95% CIs were calculated

from conditional logistic regression models, adjusted for education, housing materials, occupation, the type of domestic fuel, and snuff depending on sex for study participants. The fully adjusted models are presented in Chapter 3.

2.9. Ethical considerations

The primary study, the JCS, was approved by the University of the Witwatersrand Medical Research Ethics Committee (M140271). Secondary data did not contain identifiable data. Permission to have access to the secondary dataset was issued by CERG, and a Data Use Agreement (DUA) signed. Ethical clearance (M141171) for the secondary data analysis specific for this study was granted by the University of the Witwatersrand Medical Research Ethics Committee before secondary data analysis was started (Appendix K).

CHAPTER 3

RESULTS

3.1. Introduction

The figures, tables, graphs are used to present the results and the key findings highlighted.

3.2. Distribution of variables in the matched case-control data

The ratio of controls to cases was 1:1. Out of 1668 study participants, there were 834 (50.0%) cases, and 834 (50.0%) controls matched according to age, place of birth and sex. The distribution of cases and controls was equal according to age, place of birth and sex. Thus, the matching was successful in this present study. 523 (50.0%) cases and 523 (50.0%) controls were males meaning that there were only 5 unmatched pairs in men because there were 528 male cases before the matching process. 311 cases and 311 controls were females. It means there were no female cases remained unmatched after the completion of the matching process, considering that there were 311 female cases before the matching process (Table 3).

Compared to HIV-negative controls, more HIV-positive patients did not have oesophageal cancer (127 controls in males and 46 controls in females). From the total of 675 oesophageal cancer cases who tested HIV negative, 421 were men and 254 women. Stratified analysis by sex showed that more controls used electric fuel than oesophageal cancer cases (111 controls in men and 60 controls in females). In the non-electric category, this study found more cases than controls. The majority of oesophageal cancer cases depended on non-electric fuels for cooking and heating with the total of 713, 443 in males and 270 in females (Table 4).

There were more females (95 cases) who had oesophageal cancer who were snuff users than males (13 cases) (Table 5). Among the non-smokers, the controls were significantly greater than oesophageal cancer cases (186 controls in males and 270 in females). More study participants cases were current light smokers than other smoking categories as there were 323 oesophageal

cancer cases in total, 269 males and 54 females. Fewer women who had oesophageal cancers were current heavy smokers (11 cases) than men (108 cases) (Table 5 and Figure 4).

In the non-drinkers, there were more controls than oesophageal cancer cases in females. In the ever drank, more patients had oesophageal cancer than controls regardless of sex. The majority of oesophageal cancer cases who were females were non-drinkers (202 cases). There were more current heavy drinkers than moderate drinkers who were oesophageal cancer cases regardless of sex (Table 6 and Figure 5).

Table 3: Distribution of demographic characteristics (%) in oesophageal cancer cases and controls for the unmatched and matched oesophageal cancer case-control data

Demographic characteristics	Males N (%)				Females N (%)			
	Unmatched data		Matched data		Unmatched data		Matched data	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
	528	1308	523	523	311	3557	311	311
Age group (Years)								
Missing	0 (0)	0 (0.0)	0 (0)	0 (0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
18 – 44	46 (8.7)	663 (50.7)	46 (8.8)	46 (8.8)	33 (10.6)	1441 (40.5)	33 (10.6)	33 (10.6)
45 – 54	168 (31.8)	283 (21.6)	168 (32.1)	168 (32.1)	77 (24.8)	930 (26.2)	77 (24.8)	77 (24.8)
55 – 64	205 (38.8)	234 (17.9)	200 (38.2)	200 (38.2)	113 (36.3)	718 (20.2)	113 (36.3)	113 (36.3)
65 – 74	109 (20.6)	128 (9.8)	109 (20.8)	109 (20.8)	88 (28.3)	468 (13.2)	88 (28.3)	88 (28.3)
P value	<0.0001		<0.0001		<0.0001		<0.0001	
Place of birth								
Missing	0 (0)	2 (0.2)	0 (0)	0 (0)	0 (0)	5 (0.1)	0 (0)	0 (0)
Urban	237 (44.9)	662 (50.7)	232 (44.4)	232 (44.4)	99 (31.8)	1978 (55.6)	99 (31.8)	99 (31.8)
Rural	291 (55.1)	644 (49.3)	291 (55.6)	291 (55.6)	212 (68.2)	1574 (44.3)	212 (68.2)	212 (68.2)
P value	0.024		0.0099		<0.0001		<0.0001	
Language								
Missing	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	5 (0.1)	0 (0.0)	0 (0.0)
Zulu	89 (16.9)	337 (27.8)	89 (17.0)	119 (22.8)	46 (14.8)	884 (24.9)	46 (14.8)	69 (22.2)
Xhosa	65 (12.3)	144 (11.0)	65 (12.4)	49 (9.4)	53 (17.0)	479 (13.5)	53 (17.0)	40 (12.9)
Sotho	85 (16.1)	173 (13.2)	81 (15.5)	75 (14.3)	38 (12.2)	681 (19.2)	38 (12.2)	57 (18.3)
Tswana	154 (29.2)	179 (13.7)	154 (29.5)	91 (17.4)	99 (31.8)	679 (19.1)	99 (31.8)	64 (20.6)
Others	134 (25.4)	475 (36.3)	133 (25.4)	189 (36.1)	75 (24.1)	829 (23.3)	75 (24.1)	81 (26.1)
P value	<0.0001		<0.0001		<0.0001		<0.0001	
Marital status								
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.2)	0 (0.0)	1 (0.3)
Single/never married	64 (12.1)	242 (18.5)	63 (12.1)	33 (6.3)	60 (19.3)	642 (18.1)	60 (19.3)	29 (9.3)
Married/living together	344 (65.2)	862 (65.9)	341 (65.2)	391 (74.8)	125 (40.2)	1730 (48.8)	125 (40.2)	133 (42.8)
Widowed	59 (11.2)	79 (6.0)	59 (11.3)	51 (9.8)	92 (29.6)	636 (17.9)	92 (29.6)	96 (30.9)
Separated	61 (11.6)	125 (9.6)	60 (11.5)	48 (9.2)	34 (10.9)	541 (15.2)	34 (10.9)	52 (16.7)
P value	<0.0001		<0.0001		<0.0001		<0.0001	

Keys: Cases (oesophageal cancer), Controls (smoking and alcohol use unrelated cancers). Chi-squared test was done in the unmatched data. McNemar's chi-squared or symmetry test was done in the matched data.

Table 4: Distribution of socioeconomic status and medical condition (%) in oesophageal cancer cases and controls for the unmatched and matched oesophageal cancer case-control data

Socioeconomic status and medical condition	Males N (%)				Females N (%)			
	Unmatched data		Matched data		Unmatched data		Matched data	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
	528	1308	523	523	311	3557	311	311
Education								
Missing	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	3 (1.0)	8 (0.2)	3 (1.0)	0 (0.0)
Tertiary	31 (5.9)	283 (21.6)	30 (5.7)	67 (12.8)	5 (1.6)	684 (19.3)	5 (1.6)	26 (8.4)
Non-education	96 (18.2)	116 (8.9)	95 (18.2)	71 (13.6)	64 (20.6)	321 (9.0)	64 (20.6)	60 (19.3)
Primary	186 (35.2)	277 (21.2)	185 (35.4)	139 (26.6)	115 (37.0)	652 (18.4)	115 (37.0)	79 (25.4)
Secondary	214 (40.5)	632 (48.3)	212 (40.5)	246 (47.0)	124 (40.0)	1892 (53.3)	124 (39.9)	146 (47.0)
P value	<0.0001		<0.0001		<0.0001		<0.0001	
Housing material								
Missing	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.3)	6 (0.2)	1 (0.3)	1 (0.3)
Brick/concrete	425 (80.5)	1073 (82.1)	420 (80.3)	446 (85.3)	232 (74.6)	2994 (84.3)	232 (74.6)	258 (83.0)
Non-brick/ non-concrete	96 (18.2)	229 (17.5)	96 (18.4)	74 (14.2)	68 (21.9)	527 (14.8)	68 (21.9)	49 (15.8)
Others	7 (1.3)	5 (0.4)	7 (1.3)	3 (0.6)	10 (3.2)	30 (0.8)	10 (3.2)	3 (1.0)
P value	0.083		<0.0001		<0.0001		<0.0001	
Occupation								
Missing	3 (0.6)	6 (0.5)	3 (0.6)	3 (0.6)	1 (0.3)	18 (0.5)	1 (0.3)	1 (0.3)
Non-noxious	68 (12.9)	255 (19.6)	67 (12.8)	86 (16.4)	57 (18.3)	1086 (30.7)	57 (18.3)	73 (23.5)
Potentially noxious	270 (51.1)	592 (45.5)	269 (51.4)	259 (49.5)	25 (8.0)	274 (7.7)	25 (8.0)	19 (6.1)
Others	187 (35.4)	455 (35.0)	184 (35.2)	175 (33.5)	228 (73.3)	2179 (61.6)	228 (73.3)	218 (70.1)
P value	0.002		<0.0001		<0.0001		<0.0001	
Cooking and heating fuel								
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Electric	80 (15.2)	280 (21.4)	79 (15.1)	111 (21.2)	38 (12.2)	723 (20.3)	38 (12.2)	60 (19.3)
Non-electric	447 (84.7)	1009 (77.1)	443 (84.7)	406 (77.6)	270 (86.8)	2803 (7.7)	270 (86.8)	248 (79.7)
Others	1 (0.2)	19 (1.5)	1 (0.2)	6 (1.2)	3 (1.0)	30 (0.8)	3 (1.0)	3 (1.0)
P value	<0.0001		<0.0001		0.001		<0.0001	
Indoor and outdoor domestic fuel								
Missing	1 (0.2)	1 (0.1)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Electric inside	80 (15.2)	280 (21.4)	79 (15.1)	111 (21.2)	38 (12.2)	723 (20.3)	38 (12.2)	60 (19.3)
Non-electric inside	352 (66.7)	844 (64.6)	348 (66.5)	345 (66.0)	192 (61.7)	2446 (68.8)	192 (61.7)	203 (65.3)
Non-electric outside	94 (17.8)	164 (12.6)	94 (18.0)	60 (11.5)	78 (25.1)	357 (10.0)	78 (25.1)	45 (14.5)
Others	1 (0.2)	19 (1.5)	1 (0.2)	6 (1.2)	3 (1.0)	30 (0.8)	3 (1.0)	3 (1.0)
P value	<0.0001		<0.0001		<0.0001		<0.0001	
HIV status								
Missing	61 (11.6)	84 (6.4)	60 (11.5)	36 (6.9)	27 (8.7)	137 (3.9)	27 (8.7)	10 (3.2)
Positive	43 (8.1)	565 (46.2)	42 (8.0)	127 (24.3)	30 (10.0)	913 (26.7)	30 (9.7)	46 (14.8)
Negative	424 (80.3)	659 (53.8)	421 (80.5)	360 (68.8)	254 (81.7)	2507 (73.3)	254 (81.7)	255 (82.6)
P value	<0.0001		<0.0001		<0.0001		<0.0001	

Keys: Cases (Oesophageal cancer), Controls (Smoking and alcohol use unrelated cancers). Chi-squared test or Fischer's exact test was done in the unmatched data. McNemar's chi-squared or symmetry test was done in the matched data.

Table 5: Distribution of smoking (%) in oesophageal cancer cases and controls for the unmatched and matched oesophageal cancer case-control data

Smoking	Males N (%)				Females N (%)			
	Unmatched data		Matched data		Unmatched data		Matched data	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
	528	1308	523	523	311	3557	311	311
Categorised smoking								
Missing	9 (1.7)	11 (0.8)	9 (1.7)	5 (1.0)	3 (1.0)	9 (0.3)	3 (1.0)	0 (0.0)
Non-smokers	49 (9.3)	455 (35.1)	49 (9.4)	186 (35.6)	203 (65.3)	3025 (85.3)	203 (65.3)	270 (86.8)
Current smokers								
Current light smokers	273 (51.7)	466 (35.9)	269 (51.4)	159 (30.4)	54 (17.4)	309 (8.7)	54 (17.4)	19 (6.1)
Current heavy smokers	108 (20.5)	154 (11.9)	108 (20.7)	53 (10.1)	11 (3.5)	35 (1.0)	11 (3.5)	3 (1.0)
Former smokers								
Former light smokers	67 (12.7)	149 (11.5)	67 (12.8)	76 (14.5)	34 (10.9)	155 (4.4)	34 (10.9)	16 (5.1)
Former heavy smokers	22 (4.2)	73 (5.6)	21 (4.0)	44 (8.4)	6 (1.9)	24 (0.7)	6 (1.9)	3 (1.0)
P value	<0.0001		<0.0001		<0.0001		<0.0001	
Uncategorised smoking								
Missing	9 (1.7)	11 (0.8)	9 (1.7)	5 (1.0)	3 (1.0)	9 (0.3)	3 (1.0)	0 (0.0)
Non-smokers	49 (9.3)	455 (35.1)	49 (9.4)	186 (35.6)	203 (65.3)	3025 (85.3)	203 (65.3)	270 (86.8)
Ever smoked	470 (89.0)	842 (64.9)	465 (88.9)	332 (63.5)	105 (33.8)	523 (14.7)	105 (33.8)	41 (13.2)
P value	<0.0001		0.0006		<0.0001		<0.0001	
Smoking duration (years)								
Missing	9 (1.7)	11 (0.8)	9 (1.7)	5 (1.0)	3 (1.0)	9 (0.3)	3 (1.0)	0 (0.0)
Non-smokers	49 (9.3)	455 (35.1)	49 (9.4)	186 (35.6)	203 (65.3)	3025 (85.3)	203 (65.3)	270 (86.8)
1 – 15	35 (6.6)	214 (16.5)	35 (6.7)	23 (4.4)	4 (1.3)	110 (3.1)	4 (1.3)	4 (1.3)
16 – 30	96 (18.2)	329 (25.4)	95 (18.2)	84 (16.1)	21 (6.8)	149 (4.2)	21 (6.8)	8 (2.6)
31 – 45	250 (47.4)	221 (17.0)	246 (47.0)	165 (31.6)	50 (16.1)	190 (5.4)	50 (16.1)	16 (5.1)
46 and more	89 (16.9)	78 (6.0)	9 (1.7)	60 (11.5)	30 (10.0)	74 (2.1)	30 (9.7)	13 (4.2)
P value	<0.0001		<0.0001		<0.0001		<0.0001	
Age at start smoking (years)								
Missing	9 (1.7)	11 (0.8)	9 (1.7)	5 (1.0)	3 (1.0)	9 (0.3)	3 (1.0)	0 (0.0)
Non-smokers	49 (9.3)	455 (35.1)	49 (9.4)	186 (35.6)	203 (65.3)	3025 (85.3)	203 (65.3)	270 (86.8)
7 – 15	108 (20.5)	202 (15.6)	108 (20.7)	72 (13.8)	30 (10.0)	90 (2.5)	30 (9.7)	3 (1.0)
16 – 20	186 (35.2)	371 (28.6)	184 (35.2)	151 (28.9)	42 (13.5)	226 (6.4)	42 (13.5)	20 (6.4)
21 – 25	102 (19.3)	160 (12.3)	101 (19.3)	58 (11.1)	19 (6.1)	91 (2.6)	19 (6.1)	10 (3.2)
26 and more	74 (14.0)	109 (8.4)	72 (13.8)	51 (9.8)	14 (4.5)	116 (3.3)	14 (4.5)	8 (2.6)
P value	<0.0001		<0.0001		<0.0001		<0.0001	
Years since quitting smoking (years)								
Missing	9 (1.7)	11 (0.8)	9 (1.7)	5 (1.0)	3 (1.0)	9 (0.3)	3 (1.0)	0 (0.0)
Non-smokers	49 (9.3)	455 (35.1)	49 (9.4)	186 (35.6)	203 (65.3)	3025 (85.3)	203 (65.3)	270 (86.8)
Current smokers	381 (72.2)	620 (47.8)	377 (72.1)	212 (40.5)	65 (20.9)	344 (9.7)	65 (20.9)	22 (7.1)
1 – 15	14 (2.7)	21 (1.6)	14 (2.7)	13 (2.5)	9 (2.9)	21 (0.6)	9 (2.9)	2 (0.6)
16 – 20	22 (4.2)	68 (5.2)	21 (4.0)	35 (6.7)	9 (2.9)	32 (0.9)	9 (2.9)	3 (1.0)
21 – 25	53 (10.0)	133 (10.3)	53 (10.1)	72 (13.8)	22 (7.1)	126 (3.6)	22 (7.1)	14 (4.5)
P value	<0.0001		<0.0001		<0.0001		<0.0001	
Type of cigarette								
Missing	9 (1.7)	11 (0.8)	9 (1.7)	5 (1.0)	3 (1.0)	9 (0.3)	3 (1.0)	0 (0.0)
Non-smokers	49 (9.3)	455 (35.1)	49 (9.4)	186 (35.6)	203 (65.3)	3025 (85.3)	203 (65.3)	270 (86.8)
Hand rolled	56 (10.6)	31 (2.4)	56 (10.7)	19 (3.6)	8 (2.6)	11 (0.3)	8 (2.6)	0 (0.0)
Manufactured	414 (78.4)	811 (62.5)	409 (78.2)	313 (59.9)	97 (31.2)	512 (14.4)	97 (31.2)	41 (13.2)
P value	<0.0001		<0.0001		<0.0001		<0.0001	
Snuff user								
Missing	1 (0.2)	2 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)	5 (0.1)	0 (0.0)	0 (0.0)
Never a snuff user	514 (97.4)	1259 (96.4)	509 (97.3)	492 (94.1)	216 (69.5)	2597 (73.1)	216 (69.5)	214 (68.8)
Ever a snuff user	13 (2.5)	41 (3.6)	13 (2.5)	30 (5.7)	95 (30.6)	955 (26.9)	95 (30.6)	97 (31.2)
P value	0.218		<0.0001		0.164		<0.0001	

Keys: Never smoked (<1g/day), Light smokers (1 – 14 g/day), Heavy smokers (>=15 g/day), Cases (Oesophageal cancer), Controls (Smoking and alcohol use unrelated-cancers). Chi-squared test was done in the unmatched data. McNemar's chi-squared or symmetry test was done in the matched data.

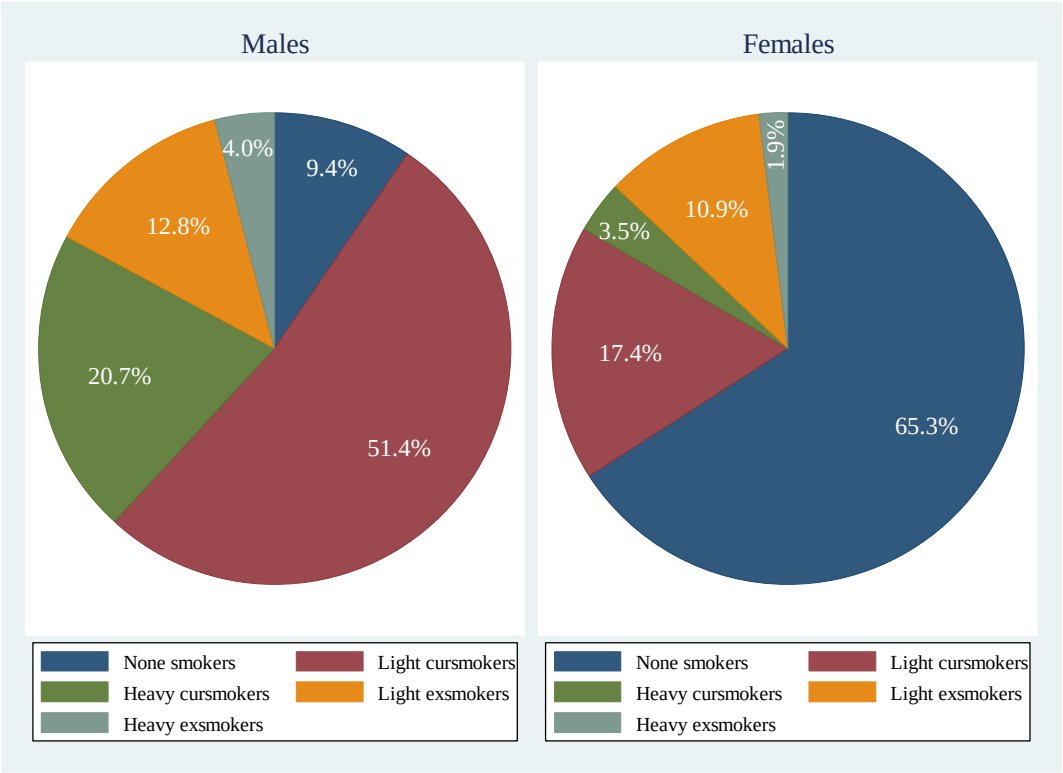

Figure 4: Graphs showing the distribution of smoking in oesophageal cancer cases stratified by sex for the matched oesophageal cancer case-control data. Keys: cursmokers (Current smokers), exsmokers (Former smokers).

Table 6: Distribution of alcohol use and interaction with tobacco use (%) in oesophageal cancer cases and controls for the unmatched and matched oesophageal cancer case-control data

Alcohol use and interaction with tobacco use	Males N (%)				Females N (%)			
	Unmatched data		Matched data		Unmatched data		Matched data	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
	528	1308	523	523	311	3557	311	311
Categorised alcohol								
Missing	14 (2.7)	10 (0.8)	14 (2.7)	4 (1.8)	3 (1.0)	19 (0.5)	3 (1.0)	3 (0.3)
Non-drinkers	138 (26.1)	403 (31.1)	137 (26.2)	183 (35.0)	202 (65.0)	2438 (68.9)	202 (65.0)	225 (72.4)
Moderate drinkers	156 (29.6)	553 (42.6)	155 (29.6)	200 (38.2)	43 (13.8)	739 (20.9)	43 (13.8)	55 (17.7)
Heavy drinkers	220 (41.7)	342 (26.4)	217 (41.5)	136 (26.0)	63 (20.3)	361 (10.2)	63 (20.3)	28 (9.0)
P value	<0.0001		<0.0001		<0.0001		<0.0001	
Uncategorised alcohol								
Missing	14 (2.7)	10 (0.8)	14 (2.7)	4 (0.8)	3 (1.0)	19 (0.5)	3 (1.0)	3 (1.0)
Non-drinkers	138 (26.1)	403 (31.1)	137 (26.2)	183 (35.0)	202 (65.0)	2438 (68.9)	202 (65.0)	225 (72.4)
Ever drank	376 (71.2)	895 (69.0)	372 (71.1)	336 (64.2)	106 (34.1)	1100 (31.1)	106 (34.1)	83 (26.7)
P value	0.078		<0.0001		0.228		<0.0001	
Categorised smoking and alcohol								
Missing	23 (4.4)	21 (1.6)	23 (4.4)	9 (1.7)	6 (1.9)	27 (0.8)	6 (1.9)	3 (1.0)
Neither smoked + neither drank	29 (5.5)	247 (19.2)	29 (5.5)	114 (21.8)	161 (51.8)	2246 (63.6)	161 (51.8)	208 (66.9)
Moderate drinkers only	9 (1.7)	147 (11.4)	9 (1.7)	50 (9.6)	24 (7.7)	574 (16.3)	24 (7.7)	44 (14.2)
Heavy drinkers only	8 (1.5)	59 (4.5)	8 (1.5)	20 (3.8)	16 (5.1)	192 (5.4)	16 (5.1)	16 (5.1)
Current light smokers only	55 (10.4)	67 (5.2)	55 (10.5)	23 (4.4)	16 (5.1)	93 (2.6)	16 (5.1)	6 (1.9)
Current light smokers + moderate drinkers	94 (17.8)	260 (20.2)	93 (17.8)	89 (17.0)	10 (3.2)	114 (3.2)	10 (3.2)	7 (2.3)
Current light smokers + heavy drinkers	116 (22.0)	136 (10.6)	113 (21.6)	46 (8.8)	28 (9.0)	99 (2.8)	28 (9.0)	5 (1.6)
Current heavy smokers only	12 (2.3)	17 (1.3)	12 (2.3)	5 (10.0)	3 (1.0)	6 (0.2)	3 (1.0)	0 (0)
Current heavy smokers +moderate drinkers	22 (4.2)	62 (4.8)	22 (4.2)	19 (3.6)	0 (0.0)	5 (0.1)	0 (0.0)	0 (0)
Current heavy smokers + heavy drinkers	72 (13.6)	74 (5.8)	72 (13.8)	28 (5.4)	7 (2.3)	24 (0.7)	7 (2.3)	3 (1.0)
Former light smokers only	29 (5.5)	44 (3.4)	29 (5.5)	24 (4.6)	18 (5.8)	78 (2.2)	18 (5.8)	10 (3.2)
Former light smokers + moderate drinkers	27 (5.1)	61 (4.7)	27 (5.2)	29 (5.5)	7 (2.3)	40 (1.1)	7 (2.3)	2 (0.6)
Former light smokers + heavy drinkers	10 (1.9)	42 (3.3)	10 (1.9)	23 (4.4)	9 (2.9)	35 (1.0)	9 (2.9)	2 (0.6)
Former heavy smokers only	9 (1.7)	24 (1.9)	8 (1.5)	14 (2.7)	3 (1.0)	10 (0.3)	3 (1.0)	1 (0.3)
Former heavy smokers + moderate drinkers	3 (0.6)	18 (1.4)	3 (0.6)	11 (2.1)	1 (0.3)	4 (0.1)	1 (0.3)	0 (0.0)
Former heavy smokers + heavy drinkers	10 (1.9)	29 (2.3)	10 (1.9)	19 (3.6)	2 (0.6)	10 (0.3)	2 (0.6)	2 (0.6)
P value	<0.0001		<0.0001		<0.0001		<0.0001	
Uncategorised smoking and alcohol								
Missing	23 (4.4)	21 (1.6)	23 (4.4)	9 (1.7)	6 (1.9)	27 (0.8)	6 (1.9)	3 (1.0)
Neither smoked + neither drank	29 (5.5)	247 (19.2)	29 (5.5)	114 (20.8)	161 (51.7)	2246 (63.6)	161 (51.8)	208 (66.9)
Only drank	17 (3.2)	206 (16.0)	17 (3.3)	70 (13.4)	40 (12.9)	766 (21.7)	40 (12.9)	60 (19.3)
Only smoked	105 (19.9)	152 (11.8)	104 (19.9)	66 (12.6)	40 (12.9)	187 (5.3)	40 (12.9)	17 (5.5)
Both smoked and drank	354 (67.1)	682 (53.0)	350 (66.9)	264 (50.5)	64 (20.6)	331 (9.4)	64 (20.6)	23 (7.4)
P value	<0.0001		<0.0001		<0.0001		<0.0001	

Keys: Non-drinkers (>1 drink per week but less than 1 drink per day). Moderate drinkers (1 – 7 drinks/week for women, 1 – 14 drinks/week for men), Heavy drinkers (8 or more drinks/week for women, 15 or more drinks/week for men). Non-smokers (<1g/day), Light smokers (1 – 14 g/day) Heavy smokers (>=15 g/day). Cases (Oesophageal cancer), Controls (Smoking and alcohol use unrelated cancers). Chi-squared test or Fisher's exact test was done in the unmatched data. McNemar's chi-squared or symmetry test was done in the matched data.

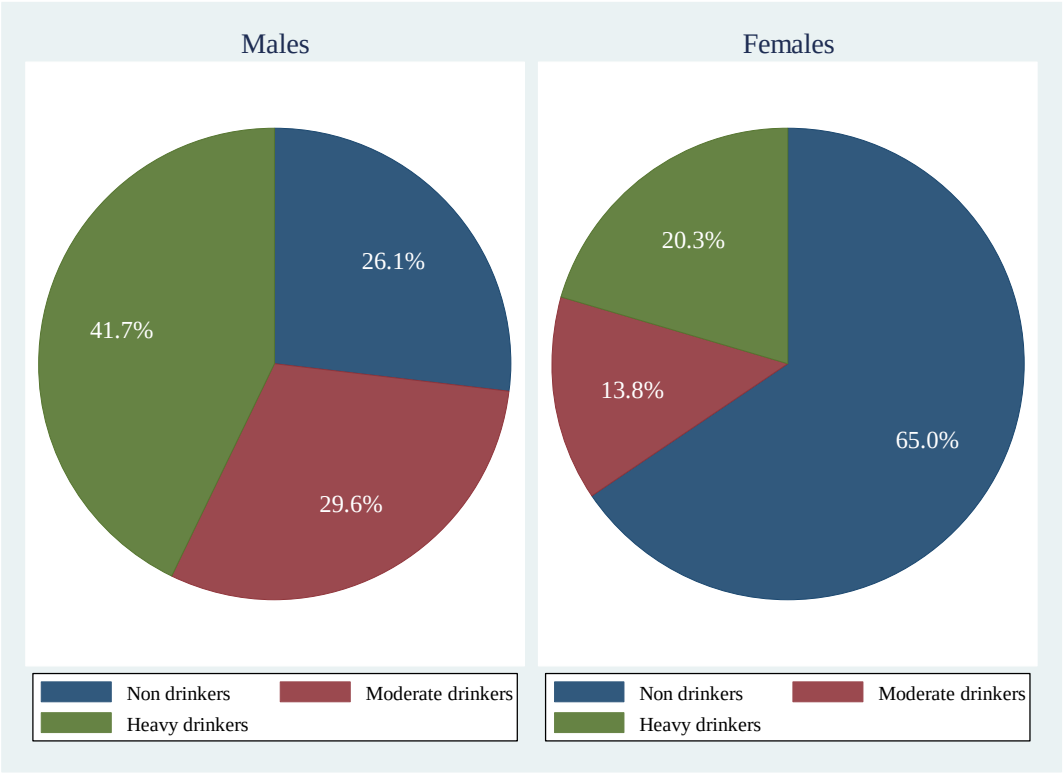

Figure 5: Graphs showing the distribution of alcohol use in oesophageal cancer cases stratified by sex for the matched oesophageal cancer case-control data

3.3. Conditional univariate analysis on oesophageal cancer

This section did not perform the conditional univariate analysis in age group, place of birth, and sex. It is because this research matched using these three variables (age, place of birth, and sex) (Appendix A). There was an independent association between education and domestic fuel with oesophageal cancer after stratified analysis by sex (Appendix B). In addition to education and domestic fuel, there was an association between housing and oesophageal cancer in females (Appendix B). This study found an association between smoking and oesophageal cancer (Appendix C). This research also found an association between snuff use with increased likelihood of oesophageal cancer in males (Appendix C). Using conditional univariate analysis, alcohol use and interaction of smoking and alcohol intake was associated with oesophageal cancer in males and females (Appendix D).

3.4. Uncategorised smoking and oesophageal cancer during conditional multivariate analysis

In the multivariate analysis, there was an increased risk of developing oesophageal cancer related to smoking without categories with highly statistically significant ($p<0.0001$) regardless of sex. Based on the observed AORs, the males who ever smoked were at higher risk of developing oesophageal cancer than smokers who were females. The observed AOR was 5.6 (95% CI: 3.7 – 8.6) in ever smokers among males and 3.4 (95% CI: 2.1 – 5.5) in ever smokers among women, respectively (Table 7 and Figure 6).

Table 7: Unconditional and conditional multivariate logistic regression models showing the association of uncategorised smoking on oesophageal cancer in the unmatched and matched oesophageal cancer case-control data

Risk factor	Males				Females			
	Unmatched data		Matched data		Unmatched data		Matched data	
	Cs/Contr 528/1308	AOR (95% CI)	Cs/Contr 523/523	AOR (95% CI)	Cs/Contr 311/3557	AOR (95% CI)	Cs/Contr 311/ 311	AOR (95% CI)
Uncategorised smoking								
Non-smokers	49/455	1.0 (Reference)	49/186	1.0 (Reference)	203/3025	1.0 (Reference)	203/270	1.0 (Reference)
Ever smoked	470/842	5.0 (3.6 – 7.1)	465/332	5.6 (3.7 – 8.6)	105/523	2.5 (1.9 – 3.3)	105/41	3.4 (2.1 – 5.5)
Age group (Years)								
18 – 44	46/663	1.0 (Reference)	Not included	Not included	33/1441	1.0 (Reference)	Not included	Not included
45 – 54	168/283	6.8 (4.7 – 9.8)			77/930	2.4 (1.5 – 3.7)		
55 – 64	205/234	9.8 (6.7 – 14.3)			113/718	4.3 (2.8 – 6.6)		
65 – 74	109/128	10.9 (7.2 – 16.7)			88/468	4.5 (2.9 – 7.0)		
Place of birth								
Urban	237/662	1.0 (Reference)	Not included	Not included	99/1978	1.0 (Reference)	Not included	Not included
Rural	291/644	1.0 (0.8 – 1.3)			212/1574	2.1 (1.6 – 3.7)		
Education								
Tertiary	31/283	1.0 (Reference)	30/67	1.0 (Reference)	5/684	1.0 (Reference)	5/26	1.0 (Reference)
Non-education	96/116	2.2 (1.3 – 3.8)	95/71	2.4 (1.3 – 4.6)	64/321	5.7 (2.2 – 14.9)	64/60	3.7 (1.2 – 11.6)
Primary	186/277	2.2 (1.4 – 3.6)	185/139	2.4 (1.4 – 4.2)	115/652	6.7 (2.6 – 17.0)	115/79	5.7 (1.9 – 16.6)
Secondary	214/632	1.6 (1.0 – 2.5)	212/246	1.5 (0.9 – 2.6)	124/1892	4.6 (1.8 – 11.5)	124/146	3.8 (1.4 – 10.3)
Housing material								
Brick/concrete	425/1073	Not included	Not included	Not included	232/2994	1.0 (Reference)	232/258	1.0 (Reference)
Non-brick/ non-concrete	96/229				68/527	1.4 (1.1 – 1.9)	68/49	1.1 (0.7 – 1.8)
Others	7/5				10/30	2.9 (1.4 – 6.5)	10/3	3.8 (1.0 – 14.6)
Occupation								
Non-noxious	68/255	1.0 (Reference)	Not included	Not included	57/1086	1.0 (Reference)	Not included	Not included
Potentially noxious	270/592	0.9 (0.6 – 1.3)			25/274	1.2 (0.7 – 2.1)		
Others	187/455	0.9 (0.7 – 1.4)			228/2179	1.2 (0.9 – 1.7)		
Cooking and heating fuel								
Electric	80/280	1.0 (Reference)	79/111	1.0 (Reference)	38/723	1.0 (Reference)	38/60	1.0 (Reference)
Non-electric	447/1009	1.2 (0.9 – 1.7)	443/406	1.2 (0.8 – 1.7)	270/2803	1.2 (0.8 – 1.7)	270/248	1.2 (0.7 – 2.1)
Others	1/19	0.3 (0.0 – 1.8)	1/6	0.2 (0.0 – 4.1)	3/30	0.9 (0.2 – 4.2)	3/3	0.8 (0.1 – 8.1)
Snuff user								
Never a snuff user	Not included	Not included	509/492	1.0 (Reference)	Not included	Not included	Not included	Not included
Ever a snuff user			13/30	0.4 (0.2 – 0.9)				
P value		<0.0001		<0.0001		<0.0001		<0.0001
Goodness of fit		0.1768				0.2095		
AUC		0.8020				0.7771		

Keys: Cs (Number of cases), Contr (Number of controls). Never smoked (<1g/day), Ever smoked (Current and ex-smokers). Unconditional logistic regression model was adjusted for age group, place of birth, education, employment and domestic fuel in males. In females, adjusted for age group, place of birth, education, housing material, employment and domestic fuel. Conditional logistic regression model was adjusted for education, housing material and domestic fuel in females. In males, adjusted for education, domestic fuel and snuff.

3.5. Categorised smoking and oesophageal cancer during conditional multivariate analysis

When the multivariate analysis was stratified by sex and categorised by smoking, heavy smoking put patients at a greater risk of developing oesophageal cancer than light smoking.

Compared to non-smokers, even light smoking increased the likelihood of oesophageal cancer regardless of sex. There was an increased risk of developing oesophageal cancer related to smoking categories with highly statistically significant ($p<0.0001$) regardless of sex. The dose-response relationship between smoking and oesophageal cancer was observed as the risk of developing oesophageal cancer was higher in current heavy smokers than current light smokers. The observed AOR was 6.3 (4.0 – 9.9) in current light smokers and 9.0 (5.2 – 15.5) in current heavy smokers among males, respectively. The observed AOR was 3.4 (95% CI: 1.9 – 6.3) in current light smokers and 5.2 (95% CI: 1.3 – 20.1) in current heavy smokers among females (Table 8 and Figure 6).

Table 8: Unconditional and conditional multivariate logistic regression models showing the association of categorised smoking on oesophageal cancer in the unmatched and matched oesophageal cancer case-control data

Risk factor	Males				Females			
	Unmatched data		Matched data		Unmatched data		Matched data	
	Cs/Contr 528/1308	AOR (95% CI)	Cs/Contr 523/523	AOR (95% CI)	Cs/Contr 311/3557	AOR (95% CI)	Cs/Contr 311/ 311	AOR (95% CI)
Categorised smoking								
Non-smokers	49/455	1.0 (Reference)	49/186	1.0 (Reference)	203/3025	1.0 (Reference)	203/270	1.0 (Reference)
Current smokers								
Current light smokers	273/466	6.5 (4.5 – 9.3)	269/159	6.3 (4.0 – 9.9)	54/309	2.5 (1.8 – 3.6)	54/19	3.4 (1.9 – 6.3)
Current heavy smokers	108/154	7.4 (4.8 – 11.5)	108/53	9.0 (5.2 – 15.5)	11/35	4.0 (1.9 – 8.4)	11/3	5.2 (1.3 – 20.1)
Former smokers								
Former light smokers	67/149	3.3 (2.1 – 5.1)	67/76	3.9 (2.3 – 6.8)	34/155	2.2 (1.4 – 3.3)	34/16	3.3 (1.6 – 6.8)
Former heavy smokers	22/73	1.5 (0.9 – 2.8)	21/44	1.6 (0.8 – 3.3)	6/24	2.4 (0.9 – 6.2)	6/3	2.7 (0.6 – 12.4)
Age group (Years)								
18 – 44	46/663	1.0 (Reference)	Not included	Not included	33/1441	1.0 (Reference)	Not included	Not included
45 – 54	168/283	7.6 (5.2 – 11.0)			77/930	2.4 (1.6 – 3.7)		
55 – 64	205/234	11.5 (7.8 – 16.8)			113/718	4.4 (2.9 – 6.7)		
65 – 74	109/128	13.7 (8.9 – 21.1)			88/468	4.5 (2.9 – 7.1)		
Place of birth								
Urban	237/662	1.0 (Reference)	Not included	Not included	99/1978	1.0 (Reference)	Not included	Not included
Rural	291/644	1.1 (0.9 – 1.5)			212/1574	2.1 (1.6 – 2.8)		
Education								
Tertiary	31/283	1.0 (Reference)	30/67	1.0 (Reference)	5/684	1.0 (Reference)	5/26	1.0 (Reference)
Non-education	96/116	2.2 (1.3 – 3.8)	95/71	2.6 (1.3 – 5.0)	64/321	5.6 (2.1 – 14.7)	64/60	3.7 (1.2 – 11.6)
Primary	186/277	2.2 (1.4 – 3.6)	185/139	2.4 (1.4 – 4.3)	115/652	6.6 (2.6 – 16.9)	115/79	5.8 (2.0 – 16.8)
Secondary	214/632	1.5 (0.9 – 2.4)	212/246	1.5 (0.9 – 2.6)	124/1892	4.6 (1.8 – 11.4)	124/146	3.8 (1.4 – 10.4)
Housing material								
Brick/concrete	Not included	Not included	Not included	Not included	232/2994	1.0 (Reference)	232/258	1.0 (Reference)
Non-brick/ non-concrete					68/527	1.4 (1.0 – 1.9)	68/49	1.1 (0.7 – 1.8)
Others					10/30	2.9 (1.3 – 6.4)	10/3	3.7 (0.9 – 14.1)
Occupation								
Non-noxious	68/255	1.0 (Reference)	Not included	Not included	57/1086	1.0 (Reference)	Not included	Not included
Potentially noxious	270/592	0.9 (0.7 – 1.4)			25/274	1.2 (0.7 – 2.1)		
Others	187/455	0.9 (0.7 – 1.4)			228/2179	1.2 (0.9 – 1.7)		
Cooking and heating fuel								
Electric	80/280	1.0 (Reference)	79/111	1.0 (Reference)	38/723	1.0 (Reference)	38/60	1.0 (Reference)
Non-electric	447/1009	1.2 (0.9 – 1.7)	443/406	1.2 (0.8 – 1.7)	270/2803	1.2 (0.8 – 1.7)	270/248	1.2 (0.7 – 2.1)
Others	1/19	0.3 (0.0 – 2.6)	1/6	0.2 (0.0 – 3.3)	3/30	0.7 (0.2 – 4.0)	3/3	0.7 (0.1 – 7.9)
Snuff user								
Never a snuff user	Not included	Not included	509/492	1.0 (Reference)	Not included	Not included	216/214	Not included
Ever a snuff user			13/30	0.4 (0.2 – 1.0)			95/97	
P value		<0.0001		<0.0001		<0.0001		<0.0001
Goodness of fit		0.0430				0.4610		
AUC		0.8204				0.7774		

Keys: Cs (Number of cases), Contr (Number of controls). Never smoked (<1g/day), Light smokers (1 – 14 g/day), Heavy smokers (>=15 g/day). Unconditional logistic regression model was adjusted for age group, place of birth, education, employment and domestic fuel in males. In females, adjusted for age group, place of birth, education, housing material, employment and domestic fuel. Conditional logistic regression model was adjusted for education, housing material and domestic fuel in females. In males, adjusted for education, domestic fuel and snuff.

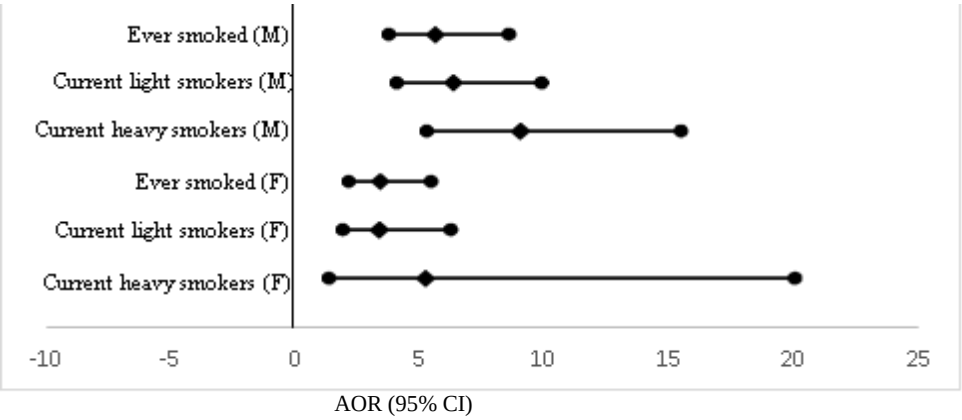

Figure 6: Risks (AORs with 95% CIs) for oesophageal cancer derived from conditional multivariate logistic regression models among smokers. Key: M (Males), F (Females), Diamond shape in the middle (Adjusted odds ratio), dot shape at the left-hand side (Lower confidence interval), dot shape at the right-hand side (Upper confidence interval).

3.6. Uncategorised alcohol use and oesophageal cancer during conditional multivariate analysis

From the multivariate analysis, there is a relationship between alcohol use and oesophageal cancer irrespective of sex with a high statistical significance ($p<0.0001$). Having ever drank had the higher risk of developing oesophageal cancer than never drank. Stratified analysis by sex revealed that the observed AOR was 1.5 (95% CI: 1.1 – 2.0) in ever drank among males and 1.3 (95% CI: 0.9 – 1.9) among females (Table 9 and Figure 7).

Table 9: Unconditional and conditional multivariate logistic regression models showing the association of uncategorised alcohol use on oesophageal cancer in the unmatched and matched oesophageal cancer case-control data

Risk factor	Males				Females			
	Unmatched data		Matched data		Unmatched data		Matched data	
	Cs/Contr 528/1308	AOR (95% CI)	Cs/Contr 523/523	AOR (95% CI)	Cs/Contr 311/3557	AOR (95% CI)	Cs/Contr 311/ 311	AOR (95% CI)
Uncategorised alcohol								
Non-drinkers	138/403	1.0 (Reference)	137/183	1.0 (Reference)	202/2438	1.0 (Reference)	202/225	1.0 (Reference)
Ever drank	376/895	1.4 (1.0 – 1.7)	372/336	1.5 (1.1 – 2.0)	106/1100	1.3 (1.0 – 1.7)	106/83	1.3 (0.9 – 1.9)
Age group (Years)								
18 – 44	46/663	1.0 (Reference)	Not included	Not included	33/1441	1.0 (Reference)	Not included	Not included
45 – 54	168/283	6.9 (4.8 – 9.9)			77/930	2.6 (1.7 – 4.0)		
55 – 64	205/234	9.9 (6.9 – 14.4)			113/718	4.7 (3.1 – 7.2)		
65 – 74	109/128	10.3 (6.8 – 15.5)			88/468	4.6 (2.9 – 7.3)		
Place of birth								
Urban	237/662	1.0 (Reference)	Not included	Not included	99/1978	1.0 (Reference)	Not included	Not included
Rural	291/644	0.9 (0.9 – 1.1)			212/1574	1.9 (1.4 – 2.5)		
Education								
Tertiary	31/283	1.0 (Reference)	30/67	1.0 (Reference)	5/684	1.0 (Reference)	5/26	1.0 (Reference)
Non-education	96/116	2.7 (1.6 – 4.6)	95/71	2.3 (1.8 – 6.0)	64/321	7.0 (2.7 – 18.4)	64/60	4.9 (1.6 – 14.7)
Primary	186/277	2.7 (1.7 – 4.2)	185/139	2.9 (1.7 – 4.9)	115/652	8.0 (3.1 – 20.3)	115/79	6.9 (2.4 – 19.2)
Secondary	214/632	1.9 (1.2 – 2.9)	212/246	1.9 (1.2 – 3.1)	124/1892	4.8 (1.9 – 11.9)	124/146	4.1 (1.5 – 10.8)
Housing material								
Brick/concrete	Not included	Not included	Not included	Not included	232/2994	1.0 (Reference)	232/258	1.0 (Reference)
Non-brick/ non-concrete					68/527	1.5 (1.1 – 2.0)	68/49	1.3 (0.8 – 2.0)
Others					10/30	2.7 (1.2 – 5.8)	10/3	2.9 (0.8 – 11.1)
Occupation								
Non-noxious	68/255	1.0 (Reference)	Not included	Not included	57/1086	1.0 (Reference)	Not included	Not included
Potentially noxious	270/592	1.0 (0.7 – 1.4)			25/274	1.3 (0.8 – 2.1)		
Others	187/455	1.1 (0.7 – 1.5)			228/2179	1.2 (0.9 – 1.7)		
Cooking and heating fuel								
Electric	80/280	1.0 (Reference)	79/111	1.0 (Reference)	38/723	1.0 (Reference)	38/60	1.0 (Reference)
Non-electric	447/1009	1.5 (1.1 – 2.0)	443/406	1.3 (0.9 – 1.9)	270/2803	1.2 (0.8 – 1.7)	270/248	1.5 (0.9 – 2.5)
Others	1/19	0.3 (0.4 – 2.5)	1/6	0.3 (0.0 – 2.7)	3/30	0.9 (0.2 – 4.3)	3/3	0.9 (0.1 – 7.5)
Snuff user								
Never a snuff user	Not included	Not included	509/492	1.0 (Reference)	Not included	Not included	Not included	Not included
Ever a snuff user			13/30	0.4 (0.2 – 0.8)				
P value		<0.0001		<0.0001		<0.0001		<0.0001
Goodness of fit		0.1928				0.6899		
AUC		0.7673				0.7683		

Keys: Cs (Number of cases), Contr (Number of controls). Non-drinkers (>1 drink per week but less than 1 drink per day). Ever drank (Moderate drinkers (1 – 7 drinks/week for women, 1 – 14 drinks/week for men), Heavy drinkers (8 or more drinks/week for women, 15 or more drinks/week for men). Unconditional logistic regression model was adjusted for age group, place of birth, education, employment and domestic fuel in males. In females, adjusted for age group, place of birth, education, housing material, employment and domestic fuel. Conditional logistic regression model was adjusted for education, housing material and domestic fuel in females. In males, adjusted for education, domestic fuel and snuff.

3.7. Categorised alcohol use and oesophageal cancer during conditional multivariate analysis

There was an association between categorised drinking and oesophageal cancer with highly statistical significance ($p<0.0001$) regardless of sex. The observed AOR was 1.1 (95% CI: 0.8 – 1.5) in moderate drinkers and 2.2 (95% CI: 1.5 – 3.1) in heavy drinkers among males. The observed AOR was 0.8 (95% CI: 0.5 – 1.3) in moderate drinkers and 2.4 (95% CI: 1.4 – 4.1) in heavy drinkers among females (Table 10 and Figure 7).

Table 10: Unconditional and conditional multivariate logistic regression models showing the association of categorised alcohol use on oesophageal cancer in the unmatched and matched oesophageal cancer case-control data

Risk factor	Males				Females			
	Unmatched data		Matched data		Unmatched data		Matched data	
	Cs/Contr 528/1308	AOR (95% CI)	Cs/Contr 523/523	AOR (95% CI)	Cs/Contr 311/3557	AOR (95% CI)	Cs/Contr 311/ 311	AOR (95% CI)
Categorised alcohol								
Non-drinkers	138/403	1.0 (Reference)	137/183	1.0 (Reference)	202/2438	1.0 (Reference)	202/225	1.0 (Reference)
Moderate drinkers	156/553	1.0 (0.8 – 1.4)	155/200	1.1 (0.8 – 1.5)	43/739	1.0 (0.6 – 1.3)	43/55	0.8 (0.5 – 1.3)
Heavy drinkers	220/342	1.9 (1.4 – 2.5)	217/136	2.2 (1.5 – 3.1)	63/361	2.1 (1.5 – 2.9)	63/28	2.4 (1.4 – 4.1)
Age group (Years)								
18 – 44	46/663	1.0 (Reference)	Not included	Not included	33/1441	1.0 (Reference)	Not included	Not included
45 – 54	168/283	6.6 (4.5 – 9.5)			77/930	2.5 (1.6 – 3.9)		
55 – 64	205/234	9.6 (6.7 – 13.9)			113/718	4.7 (3.1 – 7.1)		
65 – 74	109/128	10.0 (6.6 – 15.1)			88/468	4.6 (2.9 – 7.2)		
Place of birth								
Urban	237/662	1.0 (Reference)	Not included	Not included	99/1978	1.0 (Reference)	Not included	Not included
Rural	291/644	0.9 (0.7 – 1.2)			212/1574	1.9 (1.4 – 2.5)		
Education								
Tertiary	31/283	1.0 (Reference)	30/67	1.0 (Reference)	5/684	1.0 (Reference)	5/26	1.0 (Reference)
Non-education	96/116	2.5 (1.5 – 4.2)	95/71	2.9 (1.6 – 5.4)	64/321	6.4 (2.4 – 16.9)	64/60	5.3 (1.8 – 16.2)
Primary	186/277	2.4 (1.5 – 3.9)	185/139	2.7 (1.6 – 4.6)	115/652	7.3 (2.9 – 18.7)	115/79	7.3 (2.6 – 20.9)
Secondary	214/632	1.7 (1.1 – 2.7)	212/246	1.8 (1.1 – 3.0)	124/1892	4.5 (1.8 – 11.3)	124/146	4.4 (1.6 – 11.7)
Housing material								
Brick/concrete	Not included	Not included	Not included	Not included	232/2994	1.0 (Reference)	232/258	1.0 (Reference)
Non-brick/ non-concrete					68/527	1.4 (1.0 – 1.9)	68/49	1.2 (0.8 – 1.9)
Others					10/30	2.7 (1.2 – 5.8)	10/3	2.5 (0.7 – 9.6)
Occupation								
Non-noxious	68/255	1.0 (Reference)	Not included	Not included	57/1086	1.0 (Reference)	Not included	Not included
Potentially noxious	270/592	1.0 (0.7 – 1.5)			25/274	1.3 (0.7 – 2.1)		
Others	187/455	1.0 (0.7 – 1.5)			228/2179	1.3 (0.9 – 1.7)		
Cooking and heating fuel								
Non-Smoky	80/280	1.0 (Reference)	79/111	1.0 (Reference)	38/723	1.0 (Reference)	38/60	1.0 (Reference)
Smoky	447/1009	1.5 (1.1 – 2.0)	443/406	1.4 (1.0 – 2.0)	270/2803	1.2 (0.9 – 1.8)	270/248	1.5 (0.9 – 2.5)
Others	1/19	0.3 (0.0 – 2.6)	1/6	0.3 (0.0 – 2.5)	3/30	0.9 (0.2 – 4.3)	3/3	1.1 (0.1 – 9.3)
Snuff user								
Never snuff user	Not included	Not included	509/492	1.0 (Reference)	216/2597	Not included	Not included	Not included
Ever snuff user			13/30	0.4 (0.2 – 0.7)	95/955			
P value		<0.0001		<0.0001		<0.0001		<0.0001
Goodness of fit		0.6221				0.2456		
AUC		0.7743				0.7740		

Keys: Cs (Number of cases), Contr (Number of controls). Non-drinkers (>1 drink per week but less than 1 drink per day), Moderate drinkers (1 – 7 drinks/week for women, 1 – 14 drinks/week for men), Heavy drinkers (8 or more drinks/week for women, 15 or more drinks/week for men). Unconditional logistic regression model was adjusted for age group, place of birth, education, employment and domestic fuel in males. In females, adjusted for age group, place of birth, education, housing material, employment and domestic fuel. Conditional logistic regression model was adjusted for education, housing material and domestic fuel in females. In males, adjusted for education, domestic fuel and snuff.

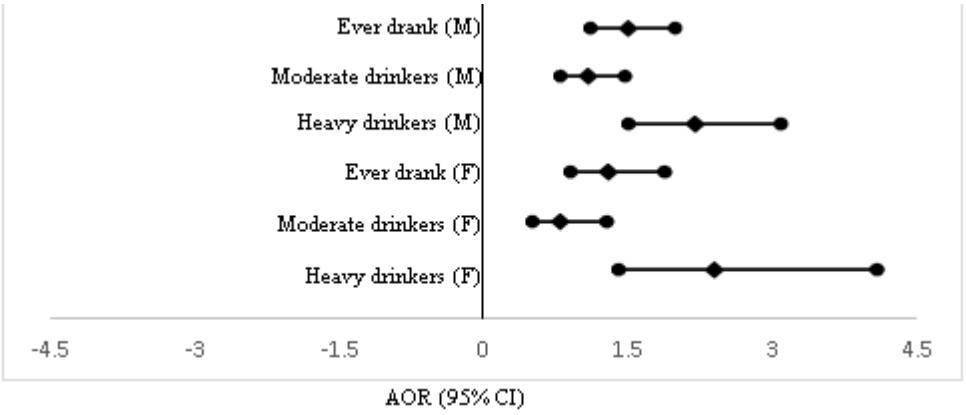

Figure 7: Risks (AORs with 95% CIs) for oesophageal cancer derived from conditional multivariate logistic regression models among alcohol drinkers. Key: M (Males), F (Females), Diamond shape in the middle (Adjusted odds ratio), dot shape at the left-hand side (Lower confidence interval), dot shape at the right-hand side (Upper confidence interval).

3.8. Uncategorised interaction of smoking and alcohol use and oesophageal cancer during conditional multivariate analysis

Combined smoking and drinking correlated with greater magnitudes of risk for oesophageal cancer among females. There was evidence of the association between the interaction of uncategorised smoking and alcohol use and oesophageal cancer ($p<0.0001$). Study participants who both smoked and drank had the higher risk of developing oesophageal cancer than oesophageal cancer cases who were only alcohol users irrespective of sex. Stratified analysis by sex revealed that the males who both smoked and drank had the AOR of 6.2 (95% CI: 3.6 – 10.8) and 1.0 (95% CI: 0.5 – 2.1) in drank only among men. This research found the similar pattern among females, except that even that only smokers had the higher likelihood of oesophageal cancer than women who were only alcohol users. The observed AOR was 2.9 (95% CI: 1.5 – 5.7) in only smokers and 0.8 (95% CI: 0.5 – 1.4) in only alcohol users among females. However, the observed AOR was 3.4 (95% CI: 1.9 – 6.2) in both smoked and drank in women (Table 11 and Figure 8).

Table 11: Unconditional and conditional multivariate logistic regression models showing the association of uncategorised interaction of smoking and alcohol use on oesophageal cancer in the unmatched and matched oesophageal cancer case-control data

Risk factor	Males				Females			
	Unmatched data		Matched data		Unmatched data		Matched data	
	Cs/Contr	AOR (95% CI)	Cs/Contr	AOR (95% CI)	Cs/Contr	AOR (95% CI)	Cs/Contr	AOR (95% CI)
	528/1308		523/523		311/3557		311/ 311	
Uncategorised smoking and alcohol								
Neither smoked + neither drank	29/247	1.0 (Reference)	29/114	1.0 (Reference)	161/2246	1.0 (Reference)	161/208	1.0 (Reference)
Only drank	17/206	1.0 (0.5 – 1.8)	17/70	1.0 (0.5 – 2.1)	40/766	1.0 (0.6 – 1.3)	40/60	0.8 (0.5 – 1.4)
Only smoked	105/152	5.8 (3.5 – 9.5)	104/66	7.6 (4.1 – 14.2)	40/187	2.1 (1.4 – 3.2)	40/17	2.9 (1.5 – 5.7)
Both smoked and drank	354/682	5.0 (3.2 – 7.8)	350/264	6.2 (3.6 – 10.8)	64/331	2.7 (1.9 – 3.7)	64/23	3.4 (1.9 – 6.2)
P value		<0.0001		<0.0001		<0.0001		<0.0001
Goodness of fit		0.1636				0.2033		
AUC		0.8036				0.7785		

Keys: Cs (Number of cases), Contr (Number of controls). Non-smokers (<1g/day), Only smoked (Light smokers (1 – 14 g/day), Heavy smokers (>=15 g/day for both current and ex-smokers). Non-drinkers (>1 drink per week but less than 1 drink per day). Only drank (Moderate drinkers (1 – 7 drinks/week for women, 1 – 14 drinks/week for men), Heavy drinkers (8 or more drinks/week for women, 15 or more drinks/week for men). Unconditional logistic regression model was adjusted for age group, place of birth, education, employment and domestic fuel in males. In females, adjusted for age group, place of birth, education, housing material, employment and domestic fuel. Conditional logistic regression model was adjusted for education, housing material and domestic fuel in females. In males, adjusted for education, domestic fuel and snuff.

3.9. Categorised interaction of smoking and alcohol use and oesophageal cancer during conditional multivariate analysis

Compared to both current light smokers and moderate drinkers, the interaction of smoking and drinking (current heavy smokers and heavy drinkers) magnified the likelihood of oesophageal cancer irrespective of sex. In females, the oesophageal cancer cases who were current heavy smokers and heavy drinkers had almost twice the risk of oesophageal cancer when compared to current light smokers and moderate drinkers. Oesophageal cancer cases who were current heavy smokers and heavy drinkers were more than twice the risk of oesophageal cancer when compared to those who were current light smokers and moderate drinkers in males. These findings were not surprising because the biochemical and biological processes are contributing to the observed pattern. Stratified analysis by sex revealed that males who were both current light smokers and moderate drinkers had the AOR of 5.4 (95% CI: 2.9 – 10.1) and 15.0 (95% CI: 7.2 – 31.3) in current heavy smokers and heavy drinkers. The observed AOR was 1.5 (95% CI: 0.5 – 4.4) in current light smokers and moderate

drinkers and 2.7 (95% CI: 0.6 – 11.2) in current heavy smokers and heavy drinkers among females (Table 12 and Figure 8).

Table 12: Unconditional and conditional multivariate logistic regression models showing the association of categorised interaction of smoking and alcohol use on oesophageal cancer in the unmatched and matched oesophageal cancer case-control data

Risk factor	Males				Females			
	Unmatched data		Matched data		Unmatched data		Matched data	
	Cs/Contr	AOR (95% CI)	Cs/Contr	AOR (95% CI)	Cs/Contr	AOR (95% CI)	Cs/Contr	AOR (95% CI)
	528/1308		523/523		311/3557		311/311	
Categorised smoking and alcohol								
Neither smoked + neither drank	29/247	1.0 (Reference)	29/114	1.0 (Reference)	161/2246	1.0 (Reference)	161/208	1.0 (Reference)
Moderate drinkers only	9/147	0.7 (0.3 – 1.6)	9/50	0.8 (0.3 – 2.1)	24/574	0.8 (0.5 – 1.2)	24/44	0.6 (0.3 – 1.2)
Heavy drinkers only	8/59	1.5 (0.6 – 3.6)	8/20	1.7 (0.6 – 5.1)	16/192	1.1 (0.6 – 2.0)	16/16	1.4 (0.6 – 3.2)
Current light smokers only	55/67	9.1 (5.0 – 16.5)	55/23	10.5 (4.8– 23.2)	16/93	2.0 (1.1 – 3.5)	16/6	2.5 (0.9 – 7.3)
Current light smokers + moderate drinkers	94/260	4.6 (2.8 – 7.7)	93/89	5.4 (2.9 – 10.1)	10/114	1.5 (0.7 – 3.0)	10/7	1.5 (0.5 – 4.4)
Current light smokers + heavy drinkers	116/136	8.6 (5.1 – 14.3)	113/46	11.0 (5.6– 21.6)	28/99	4.2 (2.6 – 6.8)	28/5	5.7 (2.1 – 15.7)
Current heavy smokers only	12/17	8.4 (3.2 – 21.7)	12/5	14.2 (4.0 – 51.1)	3/6	5.4 (1.3 – 23.5)	3/0	0
Current heavy smokers + moderate drinkers	22/62	4.2 (2.1 – 8.4)	22/19	6.1 (2.5 – 15.1)	0/5	–	0/0	0
Current heavy smokers + heavy drinkers	72/74	10.3 (5.8 – 18.2)	72/28	15.0 (7.2 – 31.3)	7/24	3.7 (1.5 – 9.4)	7/3	2.7 (0.6 – 11.2)
Former light smokers only	29/44	5.2 (2.7 – 10.1)	29/24	7.7 (3.4 – 17.6)	18/78	2.0 (1.1 – 3.6)	18/10	2.8 (1.1 – 7.1)
Former light smokers + moderate drinkers	27/61	3.6 (1.9 – 6.9)	27/29	3.6 (1.7 – 7.8)	7/40	1.9 (0.8 – 4.5)	7/2	3.8 (0.8 – 17.7)
Former light smokers + heavy drinkers	10/42	1.6 (0.7 – 3.7)	10/23	3.1 (1.2 – 8.1)	9/35	2.6 (1.2 – 5.7)	9/2	4.4 (0.9 – 22.2)
Former heavy smokers only	9/24	1.7 (0.7 – 4.2)	8/14	1.6 (0.5 – 4.6)	3/10	2.1 (0.6 – 8.1)	3/1	4.5 (0.4 – 50.4)
Former heavy smokers + moderate drinkers	3/18	1.0 (0.3 – 3.6)	3/11	1.5 (0.3 – 6.8)	1/4	3.3 (0.3 – 33.4)	1/0	0
Former heavy smokers + heavy drinkers	10/29	1.9 (0.8 – 4.5)	10/19	2.5 (0.9 – 7.0)	2/10	2.4 (0.5 – 11.8)	2/2	1.7 (0.2 – 15.5)
P value		<0.0001		<0.0001		<0.0001		<0.0001
Goodness of fit		0.0019				0.8444		
AUC		0.8285				0.7834		

Keys: Cs (Number of cases), Contr (Number of controls). Never smoked (<1g/day), Light smokers (1 – 14 g/day), Heavy smokers (>=15 g/day). Non-drinkers (>1 drink per week but less than 1 drink per day), Moderate drinkers (1 – 7 drinks/week for women, 1 – 14 drinks/week for men), Heavy drinkers (8 or more drinks/week for women, 15 or more drinks/week for men). Unconditional logistic regression model was adjusted for age group, place of birth, education, employment and domestic fuel in males. In females, adjusted for age group, place of birth, education, housing material, employment and domestic fuel. Conditional logistic regression model was adjusted for education, housing material and domestic fuel in females. In males, adjusted for education, domestic fuel and snuff.

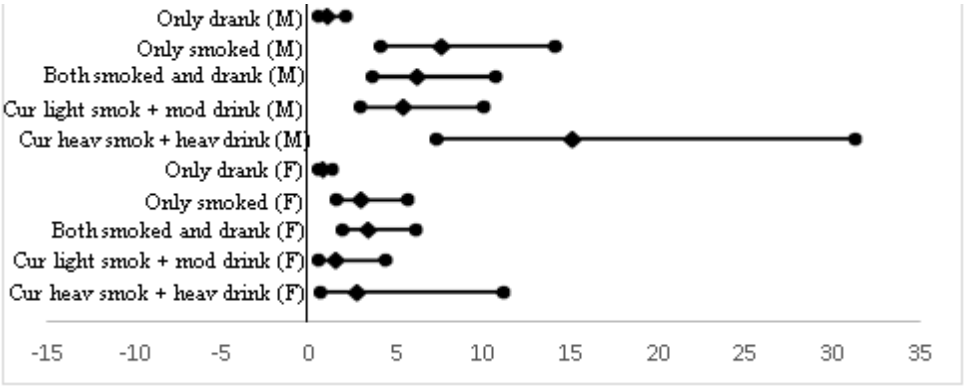

Figure 8: Risks (AORs with 95% CIs) for oesophageal cancer in relation to the interaction of smoking and alcohol use derived from conditional multivariate logistic regression models. Key: Cur light smok + Mod drink (Current light smokers + Moderate drinkers), Cur heav smok + Heav drink (Heavy drinkers + Current heavy smokers). M (Males), F (Females). Diamond shape in the middle (Adjusted odds ratio), dot shape at the left-hand side (Lower confidence interval), dot shape at the right-hand side (Upper confidence interval).

CHAPTER 4

DISCUSSION

4.1. Introduction

This section discusses the findings obtained from the secondary data analysis in details. Moreover, this chapter also compares the results of this study with other published studies. This chapter also discusses the association of lifestyle and oesophageal cancer where the focus was on smoking and alcohol consumption although using a snuff is part of the lifestyle component. The other factors such as demographic characteristics and socioeconomic status are associated with oesophageal cancer, and therefore this section also discusses them. This chapter ends with the discussion of strengths and limitations of the study.

4.2. Lifestyle

The discussion of findings obtained from the secondary data analysis relates to objective 1 and 2 of this study. The focus of the study was on the association of lifestyle risk factors and oesophageal cancer. Considering that oesophageal cancer is a multifactorial process, therefore this study did not ignore the other risk factors such as demographic characteristics and socioeconomic status. The association of lifestyle and other risk factors with oesophageal cancer is discussed.

4.2.1. Association of smoking and oesophageal cancer

It was noteworthy that the resulted AORs increased during stratified analysis by sex for the matched case-control study. Compared to non-smokers individuals, men and women smokers were 5.6 (95% CI: 3.7 – 8.6) and 3.4 (95% CI: 2.1 – 5.5) times more likely to have oesophageal cancer during conditional logistic regression. These findings suggested that men were at higher risk of getting oesophageal cancer than women. It is because the smoking habit is more prevalent in men than women in blacks. It is not a surprising fact because few women were smoking as stated previously that the majority of women were non-smokers. Altogether

the study findings showed a strong dose–response relationship between smoking and oesophageal cancer as the resulted AORs were higher among current heavy smokers than current light smokers regardless of sex. These results suggested that that tobacco smoking had an association with increased risk of oesophageal cancer. Some studies reported that the amount of cigarette has a positive correlation with oesophageal cancer (59, 94, 95). The dose is the important contributor here. This present study also found the positive correlation between the number of cigarettes and oesophageal cancer as there was an increased risk of getting oesophageal cancer among study participants who were heavy smokers compared to those who were light smokers.

4.2.2. Association of types of cigarettes and oesophageal cancer

Study participants used different types of cigarettes, either hand rolled or manufactured cigarettes. Few oesophageal cancer cases were using the hand-rolled cigarette, and most oesophageal cancer cases were using the manufactured cigarettes (409 men and 97 women) in the matched case-control study. Of the 64 oesophageal cancer cases who were using hand-rolled cigarettes, 56 were males, and 8 were females in the matched case-control data. However, there is a fear for underreporting concerning the number of study participants who were using hand-rolled cigarette because some hand rolled cigarettes are illegal in South Africa (96).

For the matched case-control data, the study participants who used hand-rolled cigarettes were at higher risk of developing oesophageal cancer, compared to those who were using manufactured cigarettes. However, this was not a surprising fact because the hand rolled cigarettes have the high content of compounds such as benzopyrene and benzene (97). There is evidence that benzopyrene and benzene are carcinogens (97).

The findings here are consistency with the studies that were conducted both in African and Westernized countries (59, 98, 99). The differences between manufactured and hand-rolled

cigarette are noteworthy. In manufactured cigarettes, the weight, diameter, packing density of the tobacco and the porosity of the wrapping paper is controlled by the companies producing it, whereas in hand rolled cigarette these particular elements are controlled by the smoker (100, 101). In South Africa, most often the hand-rolled cigarette smokers use newspaper without filters to roll their cigarettes which increase the danger of smoking (100, 102). These may suggest that hand rolled cigarette smoking leads to more puffs, and inhalation of more smoke per cigarette with long periods (101). Furthermore, some studies found that manufactured cigarette smokers were more likely to make attempts at quitting than hand-rolled cigarettes smokers (103, 104).

4.2.3. Association of duration of smoking, years since stopping smoking and age at started smoking and oesophageal cancer

In the matched case-control data, there were few cases with a smoking length of 1 – 15 years (35 in males, 4 in females). The majority of oesophageal cancer cases had a smoking length of 31 – 45 years with the total of 296 cases, 246 cases in males and 50 cases in females. This present study also found that length of smoking by years increased the likelihood of oesophageal cancer. These findings are consistency with what other researchers found (46). Quitting smoking decreased the high risk of oesophageal cancer. There was a significant reduction in the risk of oesophageal cancer and the time since quitting. Current smoking increased the risk of oesophageal cancer to a greater extent than former smokers. Such findings are consistency with several case-control studies done previously (46, 105-108). Furthermore, the age when someone starts smoking also seems to decrease the risk of oesophageal cancer where those who started smoking at the age of 7 – 15 years were at a higher risk of getting oesophageal cancer compared with those who started smoking at the age of 16 – 20 years. These findings are also in agreement with the case-control done by other researchers (46, 109).

4.2.4. Association of snuff use and oesophageal cancer

Snuff is a smokeless tobacco made from ground or pulverised tobacco leaves that is inhaled into the nasal cavity, delivering a swift hit of nicotine. The majority of oesophageal cancer cases who were snuff users were females in the matched case-control data (95 in women and 13 in men). Based on the observed AOR for the matched case-control data, the AOR of 0.4 (95% CI: 0.2 – 0.9) showed that the snuff appeared almost protective against oesophageal cancer in males. These findings are in agreement with other studies that also reported no relationship between the use of snuff and oesophageal cancer (110, 111). Snuff has a lower content of carcinogenic tobacco-specific nitrosamines than the cigarette, but it seems unlikely to be protective. Other studies have found an association between snuff and oesophageal cancer (59, 111, 112). This aspect of the study is still up for debate. The possible explanation for the discrepancy in these particular findings could be because of small sample power. Therefore, more studies with sufficient sample power would be required to establish if the use of snuff has a role to play in the aetiogenesis of oesophageal cancer or not.

4.2.5. Association of alcohol use and oesophageal cancer

For the matched case-control study, the majority of females with oesophageal cancer were non-drinkers (202 cases). The observed AORs for alcohol consumption was higher than in non-drinkers in males and females. These findings suggested that alcohol drinkers are at a greater risk of getting oesophageal cancer than in non-drinkers. Compared to individuals who have not ever drank, men and women who have ever consumed alcohol were 1.5 (95% CI: 1.1 – 2.0) and 1.3 (95% CI: 0.9 – 1.9) times more likely to have oesophageal cancer in the matched case-control study, respectively. This study showed that the AOR increased during conditional logistic regression in men.

For the matched case-control data, the data revealed that there were more heavy drinkers than moderate drinkers who were cases, regardless of sex. Comparing heavy drinkers who were

oesophageal cancer cases between males and females, there were more heavy drinkers in men (217 cases) than women (63 cases). This pattern observed was expected because most of the men take riskier behaviours than women (113). Comparing AORs for unmatched and matched analysis during the stratified analysis by sex, the resulting AORs were higher in conditional logistic regression than in unconditional logistic regression. In men and women, heavy drinkers were 2.2 (95% CI: 1.5 – 3.1) and 2.4 (95% CI: 1.4 – 4.1) times more likely to get oesophageal cancer than non-drinkers in the matched case-control study. Altogether this study found that alcohol use is associated with oesophageal cancer. This study did not look at the type of alcohol drank, but it grouped alcohol based on the number of drinks taken per week. In terms of composition, ethanol is a standard component in all alcohols. But there are other components or contaminants namely N-nitrosamines and urethane in the alcohol that are suspected to increase the risk of getting oesophageal cancer as they have carcinogenic properties (59). Researchers have reported that practically findings have shown that there is the greatest risk of oesophageal cancer in the hard liquors. This is consistent with evidence that the concentration of ethanol plays an important role in alcohol-related tumours of the upper digestive tract (114). The present study also found a similar trend which is not only due to systematic effect, but there are also biochemical processes that take place within the system or body for drinkers.

From a biochemistry point of view, the ethanol changes into acetaldehyde in saliva. The acetaldehyde can then possess a promoting effect that is achieved by either solubilising tobacco-specific carcinogens or enhancing their penetration into the oesophageal mucosa, by nutritional deficiencies associated with heavy drinking or by other mechanisms which could be direct toxic or have the oxidative effect on the epithelial mucosa (115). Beers from maize and millet may contain fungi contamination which may increase the risk of oesophageal cancer. A study in Eastern Cape (a province in South Africa) found that contaminated fungi, including fumonisins, are associated with oesophageal cancer (116).

This present study did not assess the association of the duration of alcohol consumed, age at starting to drink, and years since quitting drinking on oesophageal cancer. It is because there were no variables in the secondary dataset related to the duration of alcohol consumed. Some researchers have reported that longer since quitting decreased the risk of oesophageal cancer (46, 47, 117, 111). However, this particular aspect of the study is still up for debate as some researchers found that quitting drinking does not necessarily reduce the risk for oesophageal cancer (118, 119). In addition, some researchers found an association between the duration of alcohol consumed and oesophageal cancer (59), and that age at starting to drink is not associated with oesophageal cancer (46, 59).

4.2.6. Association of interaction of smoking and alcohol use and oesophageal cancer

This study sought to determine whether the interaction of tobacco and alcohol use can act synergistically to increase the likelihood of oesophageal cancer. Therefore, this present study assessed the different combinations of these two exposures (tobacco and alcohol use) on risk of developing oesophageal cancer. Among oesophageal cancer cases, there were more males (350 cases) who both smoked and drank, compared to females (64 cases) in the matched case-control study.

Conditional logistic regression in males showed that the odds of oesophageal cancer among having both ever smoked with ever used alcohol were 6.2 (95% CI: 3.6 – 10.8) times as likely as among neither smoked with neither drank. In females, the odds of oesophageal cancer among both smokers with alcohol drinkers were 3.4 (95% CI: 1.9 – 6.2) times compared to neither smokers with neither drinkers during conditional logistic regression. Of note, the minority of study participants who were current heavy smokers and heavy drinkers were females. This present study confirms that there is the divergence of usage of smoking and alcohol between men and women.

Compared to individuals who were both non-smokers and non-drinkers in the matched case-control data, men and women who were both current heavy smokers and heavy drinkers were 15.0 (95% CI: 7.2 – 31.3) and 2.7 (95% CI: 0.6 – 11.2) times more likely to get oesophageal cancer, respectively. Altogether, this study found that there is an association between smoking and alcohol use on risk of developing oesophageal cancer. These findings show that those study participants who were both current heavy smokers and heavy drinkers have increased the risk of getting oesophageal cancer than those who are both current light smokers and moderate drinkers. This study further confirms that smoking and alcohol consumption interact to increase the likelihood of oesophageal cancer.

It is also noteworthy that this study found the dose-response relationship regardless of sex. What is learned based on these findings is that current heavy smoking and heavy drinking can act synergistically to increase the risk of oesophageal cancer. Thus, the resulting correlations were not just additive, but they were also multiplicative irrespective of sex in the unconditional multivariate logistic regression. These results are comparable with other studies (120, 121). These findings were expected because there are different scientific reasons that resulted in the trend seen. The causes for such trends are biochemically and biologically (122). Biochemically, acetaldehyde is the first metabolite of ethanol in alcohol, and it is also a component of tobacco smoke that was proven to have carcinogenic effects when using animal and human models (123, 124). With regards to the relationship between the salivary concentration of acetaldehyde, active smoking and ethanol consumption, the in vivo study suggested that upon the addition of active smoking during ethanol consumption, the salivary levels of acetaldehyde turned to increase by seven-fold compared with alcohol use alone. This translates to the existence of a synergistic risk effect of alcohol and smoking on upper gastrointestinal carcinogenesis (125, 126).

Given that alcohol use and smoking might be confounded by other factors such as diet, medication, poor oral health, and treatment none compliance they would be worth investigating further. There is a study that found that the combined use of alcohol and smoking had a protective effect on oesophageal cancer (127). The study that found that the combined use of alcohol and smoking had a protective effect on oesophageal cancer had a small sample power considering that there were only 40 total cases, and so why the researcher found a very imprecise estimate of synergy. There are however numerous studies from other populations that have found a synergistic effect of alcohol use and smoking on the risk of developing oesophageal cancer (123-126).

4.3. Demographic characteristics

4.3.1. Association of sex and oesophageal cancer

Males were the group most affected by oesophageal cancer (528 cases) compared to females (331 cases). OSCC cases were 88.0% while ADC cases were 12% of the total of 839 study participants diagnosed with oesophageal cancer. Of the two types oesophageal cancer, the majority are OSCC, and this finding agrees with published reports from Africa (128, 129). The oesophageal cancer among men was 1.7 times as likely as oesophageal cancer among women. Another study also found the similar trend found in this study (59). It may be that the smoking and drinking is more prevalent in males than females. Furthermore, the females are highly likely to quit drinking compared to males (130). The ratio of controls to cases was less than four in men, but it was significantly higher in women as smoking and alcohol use was more common among males than females. Having the ratio of controls to cases beyond four may lead to a little marginal increase in precision in the total population and females (131-133). However, this present study addressed this issue through randomly matching for age, place of birth and sex. These three risk factors were matched for because there is an association between them and oesophageal cancer (84, 38, 55, 56). In an attempt to increase the power of the case-control study, this study randomly matched each case study participants

with two controls study participants using age, place of birth and sex. The observed ratio of controls to cases was significantly less than two in age groups 55 – 64 and 65 – 74 in men thus 1:2 matching was practically impossible. However, to clarify the risk factors for oesophageal cancer, it was practically possible to achieve 1:1 matching. Therefore, the possibility of overmatching was avoided in this present study (85, 86).

4.3.2. Association of age and oesophageal cancer

For both unmatched and matched case-control data, the age ranged from 18 – 74 years. For the matched case-control data, the average age of the cases was 56.9 (SD±9.1) and the controls 56.2 years (SD±10.3) in males whereas the mean age of the cases was 57.8 (SD±9.8) and the controls 56.8 years (SD±11.6) in females. Therefore, years for cases and controls were comparable regardless of sex indicating that matching process was properly done. Furthermore, the distribution of cases and controls in relation to age group was identical the same irrespective of sex indicating the success of the matching in this present study. For both unmatched and matched case-control data, the elderly study participants who were 55 – 64 years were the group most affected by oesophageal cancer. This pattern was however not peculiar as oesophageal cancer is common among older adults (33, 1)**.** In addition, the AOR were higher among elderly study participants than in young study participants. These findings rhyme with other studies that found the increased risk for oesophageal cancer among older adults (33, 1). It may be that the study participants started smoking and drinking at the young age and never stopped, and then developed oesophageal cancer.

4.3.3. Association of place of birth and oesophageal cancer

For both unmatched and matched case-control data, most study participants who had oesophageal cancer were mainly born in rural areas. In the unconditional logistic regression, study participants with a rural background had higher AOR than those who were born in urban areas regardless of sex. In the unmatched case-control study, having a rural background

meant 1.6 (95% CI: 1.4 – 1.9) times more likely to get oesophageal cancer compared to urban born people. During unconditional logistic regression, having a rural background meant a 1.1 (95% CI: 0.9 – 1.5) increased likelihood of oesophageal cancer in males and 2.1 (95% CI: 1.6 – 2.8) increased risk in females. The resulted association between place of birth and oesophageal cancer meant that the study participants with a rural background started smoking and drinking in urban areas. Unhealthy behaviours such as smoking and drinking are more prevalent in urban than in rural areas (54).

4.4. Socioeconomic status

4.4.1. Association of education and oesophageal cancer

The level of schooling was calculated based on how many years the study participant spent in the academic institution. It was interesting to record that those study participants who were at tertiary school were least affected by oesophageal cancer. It may be that there was an increased awareness about oesophageal cancer among study participants who were at tertiary level. The presence of experts who alert and teach people about the risk factors for oesophageal cancer in the higher education training could also help in the reduction of risk of getting oesophageal cancer. Compared to those who were at tertiary education, the observed AOR were higher among uneducated study participants regardless of sex. These findings suggested that there is an association between low socioeconomic status and the oesophageal cancer, as non-education is the indication of low socioeconomic status. Many studies have linked the low socioeconomic and the increased risk of oesophageal cancer (38, 33).

4.4.2. Association of housing and oesophageal cancer

As mentioned earlier the walls of housing materials made of wood, tin, plastic and mud or clay were grouped under non-brick or non-concrete brick house which indicated low socioeconomic status. The brick or concrete houses meant high socioeconomic status. Both unmatched and matched case-control data showed that there were more study participants

with oesophageal cancer who were staying in brick houses than non-brick houses. These findings were not surprising because Johannesburg is the urbanised place thus many walls of the housing are bricks or concrete. The fact that study participants experienced oesophageal cancer even if they were staying in block housed suggested that other factors contributed to oesophageal cancer. Like any other chronic diseases, multiple factors are known and suspected to increase the risk of oesophageal cancer in which housing material is one of them.

Females who were staying in non-brick houses (AOR = 1.4 (95% CI: 1.1 – 1.9) had a higher risk of developing oesophageal cancer than those who were staying in brick houses. Although this present study found an association between the type of housing material and oesophageal cancer in women, this study obtained the information pertaining housing material only about the walls of the house. However, the other study reported that even the roof of the house is associated with oesophageal cancer as grass thatched houses may promote inhabitation of microorganisms such as fungi and bacteria which could be a risk factor for infection (59). Furthermore, the data here did not contain information on the size of the total living area occupied by the participants, land ownership, the source of water, and income which could give the details of the socioeconomic profile of study participants. It was thus not immediately possible to establish if there was any association between such factors and the oesophageal cancer.

4.4.3. Association of occupation and oesophageal cancer

This study showed that the majority of oesophageal cancer cases are working in Johannesburg. However, this is not astonishing as Johannesburg is the industrialised area hence job opportunities is one of the pulling factors. This present study is also comparable with one of the studies that were done in Johannesburg (25). In the potentially noxious group for the matched case-control data, there were more oesophageal cancer cases in men than in women. This pattern may be because most of the women were housewives and unemployed

as in most rural parts of Africa there is a belief that the males should be breadwinners, considering that most of the study participants were born in the countryside. Compared to individuals who were not exposed to potentially noxious, the higher AORs meant that having exposed to potentially noxious increased the likelihood of oesophageal cancer regardless of sex.

The surprising fact was that in spite of the severity of oesophageal cancer but the risk was still high among the study participants who were working with potentially noxious, and this is a major public health problem. The study done in Western countries reported that the severity of oesophageal cancer has a mortality rate of less than 5 years (134). The cases may be even higher than the ones reported in this present study. In the African context, the worrying factor may also be that some patients do not come to the hospital early enough as they resort to seeking help from traditional healers given that the data are from the hospitals. There is also a belief that going to the hospital for surgery would lead to death (59). Various studies have also found that there was an association between occupation and oesophageal cancer (59, 25, 135).

4.4.4. Association of domestic fuel and oesophageal cancer

Study participants used a range of fuel products. The electric fuel included electricity whereas non-electric category included wood, charcoal, coal, anthracite, paraffin, and gas as mentioned earlier. Both unmatched and matched case-control study showed that the majority of this study participants depended on non-electric fuel for cooking and heating. These study findings are in agreement with the other previous studies done in Africa (59, 25). Compared to patients who were exposed to electric fuel, patients who were exposed to non-electric fuel had a greater risk of developing oesophageal cancer regardless of sex. It may be that both men and women involve themselves in activities like cooking within the household using non-electric fuel. Moreover, some occupations involve a lot of cooking processes using non-

electric fuel depending on the nature of the occupation. The lengthy time spent by study participants at the working place (for those who work with non-electric fuel) may lead to prolonged exposure to non-electric fuel to increase the risk of oesophageal cancer.

4.4.5. Association of indoor and outdoor cooking and heating fuel and oesophageal cancer

Considering that not all the study participants were cooking and heating indoors thus there are some differences. This study took into account on whether the food is typically cooked outside or inside with the type of domestic fuel. Both unmatched and matched case-control data showed that the majority of study participants with oesophageal cancer used non-electric fuel indoors compared to those who used it outdoors. These findings showed that despite the fact that Johannesburg is the urbanised area with electricity, but most of the study participants relied on non-electric fuel products to cook and heat. The majority of study participants used non-electric fuel such as smoky fuel products because they are cheaper than electricity (136).

In addition, there was an association between non-electric fuel indoors and oesophageal cancer. These results were not astonishing because cooking with smoky product indoors mainly charcoal is carcinogenic (137). Furthermore, burning wood was reported by some of the studies as being probable carcinogenic as it contains hazardous substances namely benzo(a)pyrene, formaldehyde, and benzene (59, 137, 138). Exposure to such indoor air pollution is a major public health concern in South Africa on the grounds that this present study found that the majority of the patients with oesophageal cancer relied on smoky fuels for cooking and heating. Recalling that even in other parts of South Africa other than Johannesburg per se, the majority of inhabitants rely on smoky fuels for cooking and heating especially in rural areas without electricity. Most study participants had no choice to cook outdoors when they use smoky fuels because they could not afford to pay for the accommodation with ample space. That getting accommodation with a large area and non-

smoky fuel requires more money. Consequently, the study participants may use the same room for sleeping purpose where they usually cook using smoky fuels which are the indicative for low socioeconomic status.

From epidemiology point of view, the duration of exposure to such smoky fuels indoors is the issue here as it may catalyse the development of oesophageal cancer among the study participants since smoky fuels indoors is a known to increase the risk of oesophageal cancer. These findings are in agreement with some of the studies (139, 140). Moreover, cooking outdoors using electricity does not necessarily provide protection against oesophageal cancer. This aspect of the study requires further research in the high incidence area for oesophageal cancer with more study participants who were using non-electric fuel outdoors. The sample power might be the issue here as they were more study participants who used smoky fuel indoors than those who used smoky fuel outdoors.

4.5. Medical condition

4.5.1. Association of HIV and oesophageal cancer

HIV status is such an important variable considered in this study as there is high prevalence in South Africa. As consent was received from all participants in the study, it did not underestimate HIV status. Compared to HIV-positive study participants, both unmatched and matched case-control data showed that HIV-negative study participants were at higher risk of getting oesophageal cancer irrespective of sex. These suggested that being HIV-negative did not necessarily reduce the risk of experiencing oesophageal cancer among study participants. As an explanation for the HIV negative appearing to be protective that there may also be the issue of people being too ill to be interviewed for the study. It is possible that the HIV-positive individuals with oesophageal cancer got too sick and never made it to the hospital for an interview. In this present study, it is important to emphasise that the information with regards to HIV status for study participants was primarily based on the

laboratory test used (ELISA) to verify the HIV status of the study participants as mentioned earlier. There was a possibility that the bias was reduced in this study regarding the HIV status of the study participants because the laboratory test was performed to verify the HIV status of the study participants after JCS obtained the consent.

Furthermore, study participants may have a fear of stigmatisation in relation to HIV especially in the age group of study participants (study also included the youths) that is why the information with regards to HIV status for study participants was not only primarily based on the designed questionnaire. It would have been interesting to look at the family history for study participants in relation to oesophageal cancer in this present study, but the data did not have such a variable. It is because, in the study done in Kenya some cancers namely oesophageal, breast, cervix, stomach, blood, and kidney were reported to be prevalent in families of both cases and controls, where it happened that both son and father in two families had oesophageal cancer. There is also fear that the prevalence may be even higher than the one reported hence there could be an under-representation of cancer due to lack of awareness and myths about cancers as Kenya is an African country (59).

4.6. Strengths and limitations of the study

This present study has significant strengths and few limitations that are noteworthy. The advantages and constraints are divided into four categories namely; classification of exposures and outcomes, the local or global relevance of results, confounding and effect modification, and analysis deviance. For 90% of the study participants, the primary study confirmed the diagnosis by histology, haematology or cytology. In addition to the designed questionnaire, the HIV status of the study participants was verified using ELISA test after JCS obtained the consent (25). Therefore, there was a possibility that the bias was reduced pertaining HIV status due to the usage of the laboratory test. The study divided the primary exposures (smoking, alcohol use, the interaction of smoking and alcohol use) into two namely uncategorised and categorised exposures. The study participants were asked about the

frequency of smoking and alcohol use which made it possible for this study to categorise the primary exposures. In addition, the study participants who may have given up smoking were also included which enabled this study to classify the current and former smokers (those who stopped smoking more than 5 years prior the date of an interview were classified as former smokers while it classified those who smoked within 5 years of the date as current smokers).

The study reported here analysed only oesophageal cancer cases reported in a black South African population from the Johannesburg area, and there was no other population group in the secondary data. The population of Gauteng province was mainly composed of black Africans who moved from their places of origin to Johannesburg and adapt to urbanisation such as using tobacco and alcohol which are exposures of interest in this study. A limitation is that this study only captured oesophageal cancer cases reported to hospitals. It is possible that some patients may not attend hospitals and hence there might be no ongoing care seeking and they would not be included in this study. Another limitation is that some study participants could not speak because of the severity of their oesophageal cancer and thus the more advanced cases would not have been interviewed. Therefore, this particular limitation may cause bias in the recruitment of oesophageal cancer cases. As mentioned earlier, in dealing with confounding the multivariate logistic regression was used.

The observed ratio of controls to cases was significantly less than two in age groups 55 – 64 and 65 – 74 in men, thus 1:2 matching was practically impossible. However, to elucidate the risk factors for oesophageal cancer then it was practically possible to achieve 1:1 matching. Thus, this study also avoided the possibility of overmatching. This study assessed the association of smoking separately, alcohol separately, and the interaction of tobacco and alcohol use on risk of developing oesophageal cancer stratified by sex in a black South African population. There is limited information like this from Africa. Moreover, this

research also assessed many categories for the combined use of tobacco and alcohol and their risks for oesophageal cancer in which the previous studies did not evaluate them.

CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

5.1. Introduction

This chapter succinctly comments on the discussion. Finally, this section also makes the recommendations for future work based on the findings of this present study and the gaps in the published studies.

5.2. Conclusion

The high incidence of oesophageal cancer in Johannesburg is the consequence of a multifactorial process. Multiple factors were grouped into four well known and suspected risk factors for oesophageal cancer namely demographic characteristics, socioeconomic status, medical condition, and lifestyle. The conditional multiple logistic regression models revealed the important information about what degree smoking and alcohol use are contributing to the risk of developing oesophageal cancer in black South Africans.

We established that over the ten-year study period, using conditional logistic regression after adjusting for various factors, smoking and alcohol use was associated with cancer as both independently and as combined exposures. Also, there was a dose-response relationship between smoking as well as drinking and oesophageal cancer. Although tobacco use, as well as alcohol use, were associated with oesophageal cancer as independently exposures, the tobacco use was a leading risk factor for oesophageal cancer development. However, there was a significant interaction of tobacco use and alcohol drinking as they acted synergistically to increase the likelihood of oesophageal cancer among current heavy smokers and heavy drinkers. Compared to females who were both current heavy smokers and heavy drinkers, the males who were both current heavy smokers and heavy drinkers had the higher risk of developing oesophageal cancer. Males and females have differences in smoking and drinking habits leading to different risks of developing oesophageal cancer.

Although the focus of this study was on the association between lifestyle (smoking, and alcohol use both independently and combined exposures) and oesophageal cancer, other risk factors were also associated with oesophageal cancer. Therefore, it is also important to consider these other risk factors (demographic characteristic and socioeconomic status) associated with oesophageal cancer for intervention purpose. Furthermore, DAG confirms that there are many associations that exist between lifestyle and these other risk factors leading to an increased risk of oesophageal cancer. An increase in sin tax on cigarettes and alcohol use as well as increased education on the risk factors associated with the development of oesophageal cancer could be used as interventions to decrease the burden of this disease. In addition, an increase in age at which people would be permitted to buy cigarettes and alcohol as well as an increase sin tax on cigarettes and alcohol use would limit the access to cigarettes and alcohol.

5.3. Recommendations or future work

Any future studies would benefit from collecting information on biological and environmental risk factors, and investigate the association of such risk factors and oesophageal cancer. Any future studies would benefit from collecting information on socioeconomic status factors such as monthly income, the roof of housing, the number of occupants, the source of water, choice of hospital, and diet. South Africa is a country with diverse cultural practices, therefore, any future studies would also benefit from collecting information on lifestyle variables such as physical activity and hot tea as there is a known association between such factors with the risk of getting oesophageal cancer. This study only included the data from three public hospitals, therefore the data from private hospitals and other public hospitals around South Africa should be included in future studies. Maybe the incidence of oesophageal cancer would be even higher than the one reported in this study. Despite the fact that the incidence of oesophageal cancer has been significantly decreasing in the United States it remains predominant in areas of Northern China, Iran, Turkey, Kenya and

South Africa (142, 143). It would also be interesting to perform a systematic review with meta-analysis of observational studies evaluating the association of smoking and alcohol consumption and oesophageal cancer in Africa from 1999 to 2009, stratified by sex. However, the data and information are limited in the literature that is why there was a need to conduct this present study as it is evaluating the association of smoking and alcohol consumption and oesophageal in Johannesburg from 1999 to 2009, stratified by sex.

This study revealed the important epidemiological patterns of oesophageal cancer stratified by sex in South Africa. This study will be published in a peer-reviewed journal or presented at a conference. In doing so, this research will increase knowledge on this important topic and inform public health policies in South Africa in relation to smoking, alcohol consumption and other risk factors for oesophageal cancer. These tasks will be achieved after completing and submitting this research report for the purpose of Masters degree to the Faculty of Health Sciences at the University of the Witwatersrand.

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7.0. APPENDICES

Appendix A: Unconditional and conditional univariate analysis of demographic characteristics on oesophageal cancer in the unmatched and matched oesophageal cancer case-control data

Demographic characteristics	Males				Females			
	Unmatched data		Matched data		Unmatched data		Matched data	
	Cs/Contr 528/1308	AOR (95% CI)	Cs/Contr 523/523	AOR (95% CI)	Cs/Contr 311/3557	AOR (95% CI)	Cs/Contr 311/ 311	AOR (95% CI)
Age group (Years)								
18 – 44	46/663	1.0 (Reference)	46/46	–	33/1441	1.0 (Reference)	33/33	–
45 – 54	168/283	8.6 (6.0 – 12.2)	168/168	–	77/930	3.6 (2.4 – 5.5)	77/77	–
55 – 64	205/234	12.6 (8.9 – 18.0)	200/200	–	113/718	6.9 (4.6 –10.2)	113/113	–
65 – 74	109/128	12.3 (8.3 – 18.2)	109/109	–	88/468	8.2 (5.4 – 12.4)	88/88	–
P value		<0.0001		–		<0.0001		–
Place of birth								
Urban	237/662	1.0 (Reference)	232/232	–	99/1978	1.0 (Reference)	99/99	–
Rural	291/644	1.3 (1.0 – 1.5)	291/291	–	212/1574	2.7 (2.1 – 3.4)	212/212	–
P value		0.0243		–		<0.0001		–
Language								
Zulu	89/337	1.0 (Reference)	89/119	1.0 (Reference)	46/884	1.0 (Reference)	46/69	1.0 (Reference)
Xhosa	65/144	1.7 (1.2 – 2.5)	65/49	1.7 (1.1 – 2.7)	53/479	2.1 (1.4 – 3.2)	53/40	2.1 (1.1 – 3.7)
Sotho	85/173	1.9 (1.3 – 2.6)	81/75	1.5 (1.0 – 2.3)	38/681	1.1 (0.7 – 1.7)	38/57	1.0 (0.5 – 1.7)
Tswana	154/179	3.3 (2.4 – 4.5)	154/91	2.3 (1.6 – 3.5)	99/679	2.8 (1.9 – 4.0)	99/64	2.4 (1.4 – 3.9)
Others	134/475	1.1 (0.8 – 1.4)	133/189	0.9 (0.6 – 1.3)	75/829	1.7 (1.2 – 2.5)	75/81	1.5 (0.9 – 2.4)
P value		<0.0001		<0.0001		<0.0001		0.0009
Marital status								
Single/never married	64/242	1.0 (Reference)	63/33	1.0 (Reference)	60/642	1.0 (Reference)	60/29	1.0 (Reference)
Married/living together	344/862	1.5 (1.1 – 2.0)	341/391	0.4 (0.2 – 0.7)	125/1730	0.8 (0.6 – 1.1)	125/133	0.5 (0.3 – 0.8)
Widowed	59/79	2.8 (1.8 – 4.4)	59/51	0.5 (0.3 – 1.0)	92/636	1.5 (1.1 – 2.2)	92/96	0.5 (0.3 – 0.8)
Separated	61/125	1.8 (1.2 – 2.8)	60/48	0.6 (0.3 – 1.0)	34/541	0.7 (0.4 – 1.0)	34/52	0.3 (0.2 – 0.6)
P value		<0.0001		0.0007		<0.0001		0.0022

Keys: Cs (Number of cases), Contr (Number of controls), UOR (Unadjusted odds ratio). Unconditional univariate analysis was performed in the unmatched data. Conditional univariate analysis was performed in the matched data.

Appendix B: Unconditional and conditional univariate analysis of socioeconomic status and medical condition on oesophageal cancer in the unmatched and matched oesophageal cancer case-control data

Socioeconomic status and medical condition	Males				Females			
	Unmatched data		Matched data		Unmatched data		Matched data	
	Cs/Contr 528/1308	AOR (95% CI)	Cs/Contr 523/523	AOR (95% CI)	Cs/Contr 311/3557	AOR (95% CI)	Cs/Contr 311/ 311	AOR (95% CI)
Education								
Tertiary	31/283	1.0 (Reference)	30/67	1.0 (Reference)	5/684	1.0 (Reference)	5/26	1.0 (Reference)
Non-education	96/116	7.6 (4.8 – 12.0)	95/71	3.5 (2.0 – 6.2)	64/321	27.3 (10.9 – 68.4)	64/60	6.6 (2.3 – 19.2)
Primary	186/277	6.1 (4.0 – 9.3)	185/139	3.2 (1.9 – 5.2)	115/652	24.1 (9.8 – 59.5)	115/79	7.9 (2.9 – 21.7)
Secondary	214/632	3.1 (2.1 – 4.6)	212/246	2.0 (1.2 – 3.1)	124/1892	9.0 (3.7 – 22.0)	124/146	4.4 (1.7– 11.6)
P value		<0.0001		<0.0001		<0.0001		<0.0001
Housing material								
Brick/concrete	425/1073	1.0 (Reference)	420/446	1.0 (Reference)	232/2994	1.0 (Reference)	232/258	1.0 (Reference)
Non-brick/ non-concrete	96/229	1.1 (0.8 – 1.4)	96/74	1.4 (1.0 – 2.0)	68/527	1.7 (1.3 – 2.2)	68/49	1.5 (1.0 – 2.2)
Others	7/5	3.5 (1.1 – 11.2)	7/3	2.5 (0.6 – 9.7)	10/30	4.3 (2.1 – 8.9)	10/3	3.4 (0.9 – 12.5)
P value		0.0933		0.0711		<0.0001		<0.0001
Occupation								
Non-noxious	68/255	1.0 (Reference)	67/86	1.0 (Reference)	57/1086	1.0 (Reference)	57/73	1.0 (Reference)
Potentially noxious	270/592	1.7 (1.3 – 2.3)	269/259	1.3 (0.9 – 2.0)	25/274	1.7 (1.1 – 2.8)	25/19	1.7 (0.9 – 3.5)
Others	187/455	1.5 (1.1 – 2.1)	184/175	1.4 (0.9 – 2.0)	228/2179	2.0 (1.5 – 2.7)	228/218	1.3 (0.9 – 2.0)
P value		0.0017		0.2308		<0.0001		0.2033
Cooking and heating fuel								
Electric	80/280	1.0 (Reference)	79/111	1.0 (Reference)	38/723	1.0 (Reference)	38/60	1.0 (Reference)
Non-electric	447/1009	1.6 (1.2 – 2.0)	443/406	1.5 (1.1 – 2.1)	270/2803	1.8 (1.3 – 2.6)	270/248	1.8 (1.1 – 2.8)
Others	1/19	0.2 (0.0 – 1.4)	1/6	0.3 (0.0 – 2.1)	3/30	2.0 (0.6 – 6.5)	3/3	1.8 (0.3 – 9.3)
P value		0.0001		0.0053		0.0013		0.0467
Indoor and outdoor domestic fuel								
Electric inside	80/280	1.0 (Reference)	79/111	1.0 (Reference)	38/723	1.0 (Reference)	38/60	1.0 (Reference)
Non-electric inside	352/844	1.5 (1.1 – 1.9)	348/345	1.4 (1.0 – 2.0)	192/2446	1.5 (1.0 – 2.1)	192/203	1.5 (0.9 – 2.4)
Non-electric outside	94/164	2.0 (1.4 – 2.9)	94/60	2.3 (1.4 – 3.5)	78/357	4.2 (2.8 – 6.3)	78/45	2.9 (1.6 – 5.2)
Others	1/19	0.2 (0.0 – 1.4)	1/6	0.2 (0.0 – 2.0)	3/30	1.9 (0.6 – 6.5)	3/3	1.5 (0.3 – 8.0)
P value		<0.0001		0.0006		<0.0001		0.0018
HIV status								
Positive	43/565	1.0 (Reference)	42/127	1.0 (Reference)	30/913	1.0 (Reference)	30/46	1.0 (Reference)
Negative	424/659	8.5 (6.1 – 11.8)	421/360	4.1 (2.7 – 6.4)	254/2507	3.1 (2.1 – 4.5)	254/255	1.5 (0.9 – 2.5)
P value		<0.0001		<0.0001		<0.0001		0.1201

Keys: Cs (Number of cases), Contr (Number of controls), UOR (Unadjusted odds ratio). Unconditional univariate analysis was performed in the unmatched data. Conditional univariate analysis was performed in the matched data.

Appendix C: Unconditional and conditional univariate analysis of smoking on oesophageal cancer in the unmatched and matched oesophageal cancer case-control data

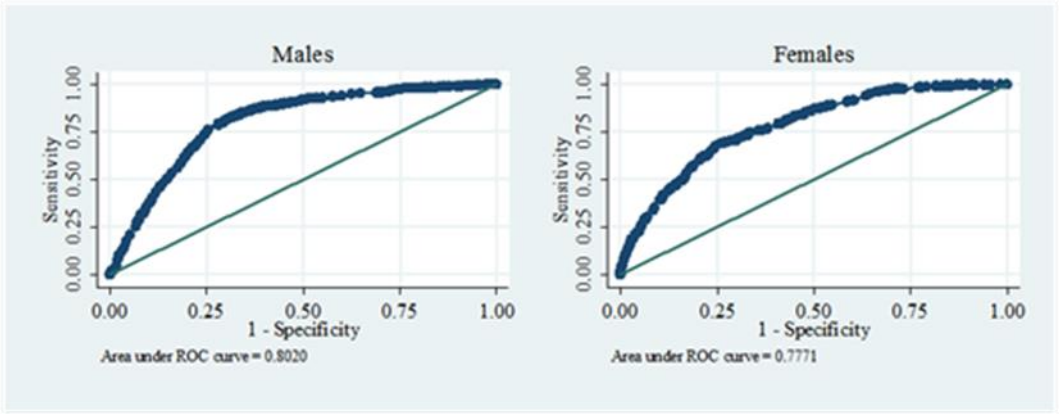
Smoking	Males				Females			
	Unmatched data		Matched data		Unmatched data		Matched data	
	Cs/Contr 528/1308	AOR (95% CI)	Cs/Contr 523/523	AOR (95% CI)	Cs/Contr 311/3557	AOR (95% CI)	Cs/Contr 311/ 311	AOR (95% CI)
Categorised smoking								
Non-smokers	49/455	1.0 (Reference)	49/186	1.0 (Reference)	203/3025	1.0 (Reference)	203/270	1.0 (Reference)
Current smokers								
Current light smokers	273/466	5.4 (3.9 – 7.6)	269/159	7.1 (4.6 – 11.1)	54/309	2.6 (1.9 – 3.6)	54/19	3.8 (2.1 – 6.7)
Current heavy smokers	108/154	6.5 (4.4 – 9.6)	108/53	9.5 (5.6 – 16.3	11/35	4.7 (2.3 – 9.4)	11/3	5.8 (1.5 – 22.1)
Former smokers								
Former light smokers	67/149	4.2 (2.7 – 6.3)	67/76	3.9 (2.3 – 6.6)	34/155	3.3 (2.2 – 4.9)	34/16	3.0 (1.5 – 5.8)
Former heavy smokers	22/73	2.8 (1.6 – 4.9)	21/44	1.9 (1.0 – 4.0)	6/24	3.7 (1.5 – 9.2)	6/3	3.2 (0.7 – 13.7)
P value		<0.0001		<0.0001		<0.0001		<0.0001
Uncategorised smoking								
Missing	49/455	1.0 (Reference)	49/186	1.0 (Reference)	203/3025	1.0 (Reference)	203/270	1.0 (Reference)
Non-smokers	470/842	5.2 (3.8 – 7.1)	465/332	6.1 (4.0 – 9.2)	105/523	3.0 (2.3 – 3.9)	105/41	3.6 (2.3 – 5.5)
Ever smoked		<0.0001		<0.0001		<0.0001		<0.0001
P value								
Smoking duration (years)								
Non-smokers	49/455	1.0 (Reference)	49/186	1.0 (Reference)	203/3025	1.0 (Reference)	203/270	1.0 (Reference)
1 – 15	35/214	1.5 (1.0 – 2.4)	35/23	6.3 (3.1 – 12.8)	4/110	0.5 (0.2 – 1.5)	4/4	1.0 (0.2 – 4.3)
16 – 30	96/329	2.7 (1.9 – 3.9)	95/84	5.0 (2.9 – 8.5)	21/149	2.1 (1.3 – 3.4)	21/8	3.9 (1.6 – 9.8)
31 – 45	250/221	10.5 (7.4– 14.8)	246/165	7.0 (4.4 – 11.2)	50/190	3.9 (2.8 – 5.5)	50/16	4.3 (2.3 – 8.4)
46 and more	89/78	10.6 (6.9 – 16.2)	9/60	5.4 (3.2 – 9.2	30/74	6.0 (3.9 – 9.4)	30/13	3.3 (1.5 – 7.4)
P value		<0.0001		<0.0001		<0.0001		<0.0001
Age at start smoking (years)								
Non-smokers	49/455	1.0 (Reference)	49/186	1.0 (Reference)	203/3025	1.0 (Reference)	203/270	1.0 (Reference)
7 – 15	108/202	5.0 (3.4 – 7.2)	108/72	6.6 (4.0 – 10.8)	30/90	5.0 (3.2 – 7.7)	30/3	13.5 (4.0 – 45.5)
16 – 20	186/371	4.7 (3.3 – 6.6)	184/151	5.2 (3.4 – 8.2)	42/226	2.8 (1.9 – 4.0)	42/20	3.0 (1.6 – 5.6)
21 – 25	102/160	6.0 (4.0 – 8.7)	101/58	7.6 (4.5 – 12.8)	19/91	3.1 (1.9 – 5.2)	19/10	2.7 (1.8 – 6.1)
26 and more	74/109	6.3 (4.2 – 9.6)	72/51	6.4 (3.7 – 11.2)	14/116	1.8 (1.0 – 3.2)	14/8	2.4 (0.9 – 6.2)
P value		<0.0001		<0.0001		<0.0001		<0.0001
Years since quitting smoking (years)								
Non-smokers	49/455	1.0 (Reference)	49/186	1.0 (Reference)	203/3025	1.0 (Reference)	203/270	1.0 (Reference)
Current smokers	381/620	5.7 (4.1 – 7.9)	377/212	7.5 (4.9 – 11.6)	65/344	2.8 (2.1 – 3.8)	65/22	4.0 (2.7 – 7.5)
1 – 15	14/21	6.2 (3.0 – 12.9)	14/13	4.5 (1.7 – 11.6)	9/21	6.4 (2.9 – 14.1)	9/2	7.5 (1.5 – 37.4)
16 – 20	22/68	3.0 (1.7 – 5.3)	21/35	2.7 (1.4 – 5.5)	9/32	4.2 (2.0 – 8.9)	9/3	4.3 (1.1 – 17.4)
21 – 25	53/133	3.7 (2.4 – 5.7)	53/72	3.1 (1.8 – 5.2)	22/126	2.6 (1.6 – 4.2)	22/14	2.3 (1.1 – 4.7)
P value		<0.0001		<0.0001		<0.0001		<0.0001
Type of cigarette								
Non-smokers	49/455	1.0 (Reference)	49/186	1.0 (Reference)	203/3025	1.0 (Reference)	203/270	1.0 (Reference
Hand rolled	56/31	16.8 (9.9 – 28.5)	56/19	12.9 (6.6 – 25.4)	8/11	10.8 (4.0 – 27.2)	8/0	0
Manufactured	414/811	4.7 (3.5 – 6.5)	409/313	5.7 (3.7 – 8.6)	97/512	2.8 (2.2 – 3.7)	97/41	3.3 (2.1 – 5.2)
P value		<0.0001		<0.0001		<0.0001		<0.0001
Snuff user								
Never a snuff user	514/1259	1.0 (Reference)	509/492	1.0 (Reference)	216/2597	1.0 (Reference)	216/214	1.0 (Reference)
Ever a snuff user	13/41	0.7 (0.4 – 1.3)	13/30	0.4 (0.2 – 0.8)	95/955	1.2 (0.9 – 1.5)	95/97	1.0 (0.7 – 1.4)
P value		0.2052		0.0070		0.1688		0.8628

Keys: Cs (Number of cases), Contr (Number of controls), UOR (Unadjusted odds ratio). Unconditional univariate analysis was performed in the unmatched data. Conditional univariate analysis was performed in the matched data.

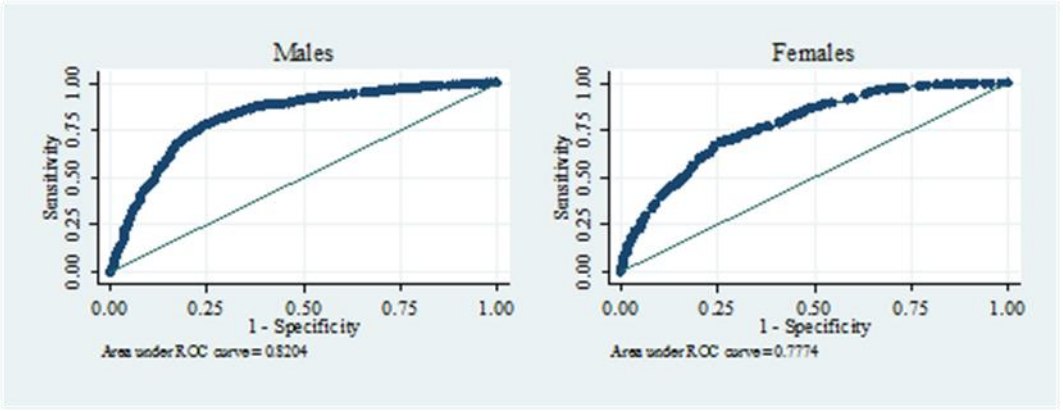
Appendix D: Unconditional and conditional univariate analysis of alcohol use and interaction with tobacco use on oesophageal cancer in the unmatched and matched oesophageal cancer case-control data

Alcohol use and interaction with tobacco use	Males				Females			
	Unmatched data		Matched data		Unmatched data		Matched data	
	Cs/Contr 528/1308	AOR (95% CI)	Cs/Contr 523/523	AOR (95% CI)	Cs/Contr 311/3557	AOR (95% CI)	Cs/Contr 311/ 311	AOR (95% CI)
Categorised alcohol								
Non-drinkers	138/403	1.0 (Reference)	137/183	1.0 (Reference)	202/2438	1.0 (Reference)	202/225	1.0 (Reference)
Moderate drinkers	156/553	0.8 (0.6 – 1.1)	155/200	1.1 (0.8 – 1.5)	43/739	0.7 (0.5 – 1.0)	43/55	0.8 (0.5 – 1.3)
Heavy drinkers	220/342	1.9 (1.5 – 2.4)	217/136	2.2 (1.6 – 3.1)	63/361	2.1 (1.6 – 2.9)	63/28	2.6 (1.6 – 4.3)
P value		<0.0001		<0.0001		<0.0001		0.0002
Uncategorised alcohol								
Non-drinkers	138/403	1.0 (Reference)	137/183	1.0 (Reference)	202/2438	1.0 (Reference)	202/225	1.0 (Reference)
Ever drank	376/895	1.2 (1.0 – 1.5)	372/336	1.5 (1.2 – 2.0)	106/1100	1.2 (0.9 – 1.5)	106/83	1.4 (1.0 – 2.0)
P value		0.0764		0.0025		0.2313		0.0456
Categorised smoking and alcohol								
Neither smoked + neither drank	29/247	1.0 (Reference)	29/114	1.0 (Reference)	161/2246	1.0 (Reference)	161/208	1.0 (Reference)
Moderate drinkers only	9/147	0.5 (0.2 – 1.1)	9/50	0.9 (0.4 – 2.2)	24/574	0.6 (0.4 – 0.9)	24/44	0.7 (0.4 – 1.2)
Heavy drinkers only	8/59	1.2 (0.5 – 2.7)	8/20	1.7 (0.6 – 4.9)	16/192	1.2 (0.7 – 2.0)	16/16	1.5 (0.7 – 3.2)
Current light smokers only	55/67	7.0 (4.1 – 11.8)	55/23	12.5 (5.7 – 27.1)	16/93	2.4 (1.4 – 4.2)	16/6	3.1 (1.2 – 8.5)
Current light smokers + moderate drinkers	94/260	3.1 (2.0 – 4.8)	93/89	6.0 (3.2 – 11.1)	10/114	1.2 (0.6 – 2.3)	10/7	1.6 (0.6 – 4.5)
Current light smokers + heavy drinkers	116/136	7.3 (4.6 – 11.5)	113/46	13.2 (6.8 – 25.5)	28/99	3.9 (2.5 – 6.2)	28/5	6.5 (2.4 – 17.4)
Current heavy smokers only	12/17	6.0 (2.6 – 13.8)	12/5	15.1 (4.3 – 52.8)	3/6	7.0 (1.7 – 28.1)	3/0	0
Current heavy smokers +moderate drinkers	22/62	3.0 (1.6 – 5.6)	22/19	6.7 (2.8 – 15.9)	0/5	0	0/0	0
Current heavy smokers + heavy drinkers	72/74	8.3 (5.0 – 13.7)	72/28	16.1 (7.8 – 33.4)	7/24	4.0 (1.7 – 9.6)	7/3	2.7 (0.6 – 11.4)
Former light smokers only	29/44	5.6 (3.1 – 10.3)	29/24	8.0 (3.5 – 17.9)	18/78	3.2 (1.9 – 5.5)	18/10	2.5 (1.1 – 5.8)
Former light smokers + moderate drinkers	27/61	3.8 (2.1 – 6.1)	27/29	3.9 (1.8 – 8.3)	7/40	2.4 (1.1 - 5.5)	7/2	2.9 (0.7 – 12.2)
Former light smokers + heavy drinkers	10/42	2.0 (0.9 – 4.5)	10/23	2.9 (1.1 – 7.4)	9/35	3.6 (1.7 – 7.6)	9/2	4.8 (1.0 – 22.9)
Former heavy smokers only	9/24	3.2 (1.4 – 7.5)	8/14	1.9 (0.7 – 5.5)	3/10	4.2 (1.1 – 15.4)	3/1	3.9 (0.4 – 42.2)
Former heavy smokers +moderate drinkers	3/18	1.4 (0.4 – 5.1)	3/11	1.6 (0.4 – 7.0)	1/4	3.5 (0.4 – 31.4)	1/0	0
Former heavy smokers + heavy drinkers	10/29	2.9 (1.3 – 6.6)	10/19	3.1 (1.2 – 8.4)	2/10	2.8 (0.6 – 12.8)	2/2	2.1 (0.2 – 20.3)
P value		<0.0001		<0.0001		<0.0001		<0.0001
Uncategorised smoking and alcohol								
Neither smoked + neither drank	29/247	1.0 (Reference)	29/114	1.0 (Reference)	161/2246	1.0 (Reference)	161/208	1.0 (Reference)
Only drank	17/206	0.7 (0.4 – 1.3)	17/70	1.1 (0.5 – 2.2)	40/766	0.7 (0.5 – 1.0)	40/60	0.9 (0.5 – 1.4)
Only smoked	105/152	5.9 (3.7 – 9.3)	104/66	8.5 (4.6 – 15.6)	40/187	3.0 (2.0 – 4.4)	40/17	3.1 (1.6 – 5.7)
Both smoked and drank	354/682	4.4 (2.9 – 6.6)	350/264	6.9 (4.0 – 12.0)	64/331	2.7 (2.0 – 3.7)	64/23	3.7 (2.1 – 6.5)
P value		<0.0001		<0.0001		<0.0001		<0.0001

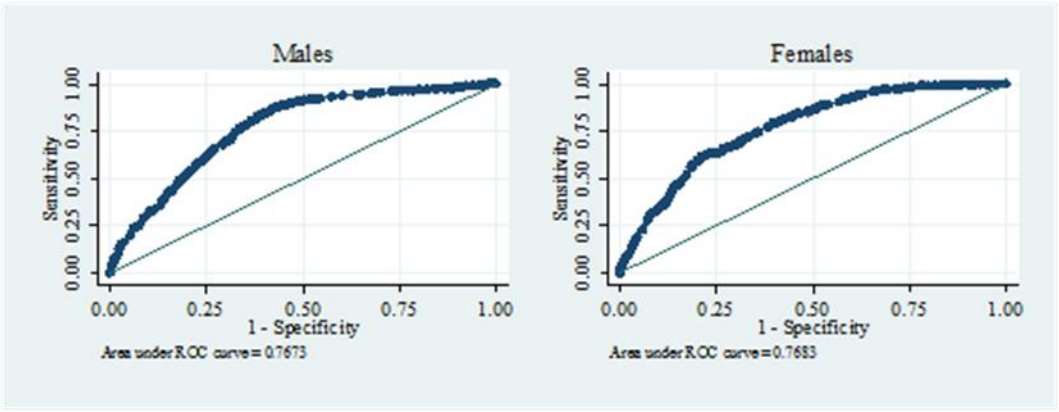
Keys: Cs (Number of cases), Contr (Number of controls) UOR (Unadjusted odds ratio). Non-drinkers (>1 drink per week but less than 1 drink per day). Moderate drinkers (1 – 7 drinks/week for women, 1 – 14 drinks/week for men), Heavy drinkers (8 or more drinks/week for women, 15 or more drinks/week for men). Non-smokers (<1g/day), Light smokers (1 – 14 g/day), Heavy smokers (>=15 g/day). Unconditional univariate analysis was performed in the unmatched data. Conditional univariate analysis was performed in the matched data.



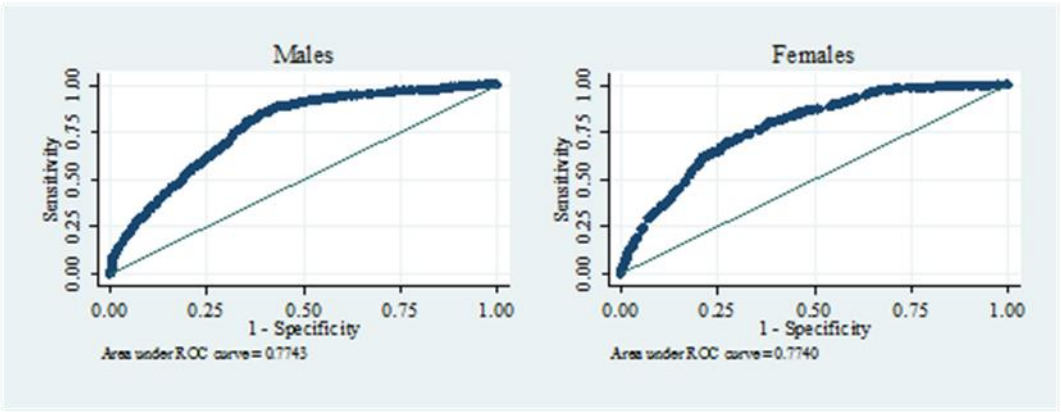
Appendix E: ROC curves for the unconditional multivariate logistic regression models showing the association uncategorised smoking and oesophageal cancer. Keys: Smoking (Non-smokers, Ever smoked).



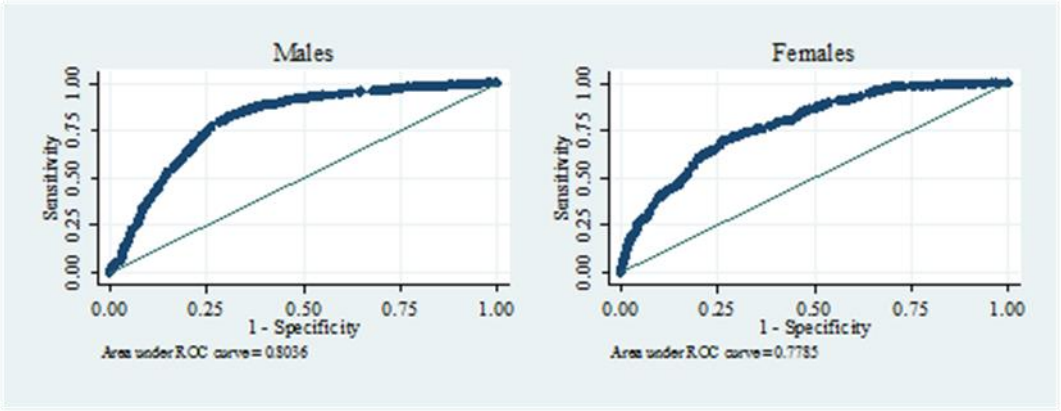
Appendix F: ROC curves for the unconditional multivariate logistic regression models showing the association of categorised smoking and oesophageal cancer. Keys: Smoking (Non-smokers, Light smokers, Heavy smokers).



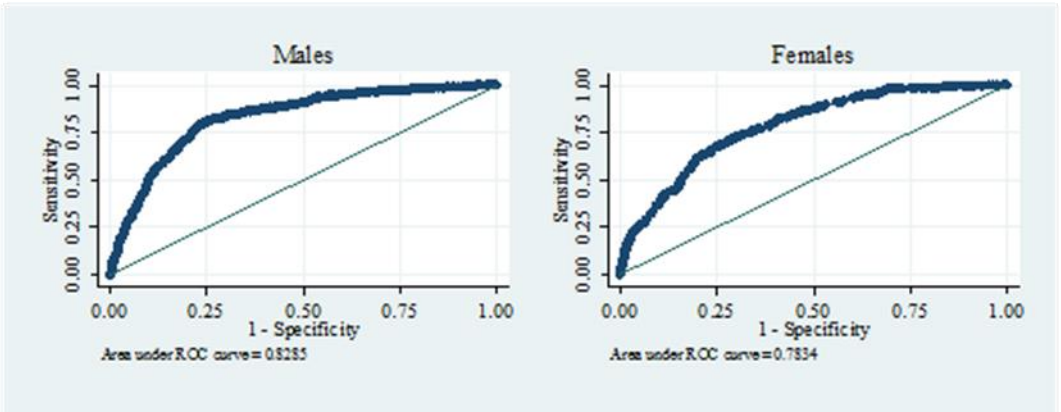
Appendix G: ROC curves for the unconditional multivariate logistic regression models showing the association of uncategorised alcohol use and oesophageal cancer. Keys: Alcohol (Never drank, Ever drank).



Appendix H: ROC curves for the unconditional multivariate logistic regression models showing the association of categorised alcohol use and oesophageal cancer. Keys: Alcohol (Non-smokers, Moderate drinkers, Heavy drinkers).



Appendix I: ROC curves for the unconditional multivariate logistic regression models showing the association of uncategorised interaction of smoking and alcohol use and oesophageal cancer. Keys: Interaction of smoking and alcohol use (Neither smoked + neither drank, Only drank, Only smoked, Both smoked and drank).



Appendix J: ROC curves for the unconditional multivariate logistic regression models showing the association of categorised interaction of smoking and alcohol use and oesophageal cancer. Interaction of smoking and alcohol use (Neither smoked + neither drank, Moderate drinkers only, Heavy drinkers only, Light current smokers only, Light current smokers + moderate drinkers, Light current smokers + heavy drinkers, Heavy current smokers only, Heavy current smokers + moderate drinkers, Heavy current smokers + Heavy drinkers, Light ex-smokers only, Light ex-smokers + moderate drinkers, Light ex-smokers + heavy drinkers, Heavy ex-smokers only, Heavy ex-smokers + moderate drinkers, Heavy ex-smokers + heavy drinkers.

Appendix K: Ethical clearance for this study (University of the Witwatersrand Medical Research Ethics Committee)

R14/49 Mr Mandlakayise Lucky Nhleko and Dr Chantal Babb

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M141171

NAME: (Principal Investigator)	Mr Mandlakayise Lucky Nhleko and Dr Chantal Babb
DEPARTMENT:	School of Public Health Division of Biostatictics and Epidemiology
PROJECT TITLE:	Effects of Smoking and Alcohol Use on Oesophageal Cancer amongst 18 to 74 Year Black South Africans in Johanneburg from 1999 - 2009
DATE CONSIDERED:	28/11/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Eustasius Musenge
APPROVED BY:	Professor Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	01/12/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature

Date 13/01/2015

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES