SKIN CANCER RISK FACTORS IN BLACK SOUTH AFRICANS, THE JOHANNESBURG CANCER STUDY: 1995 – 2016

Babongile Confidence Ndlovu

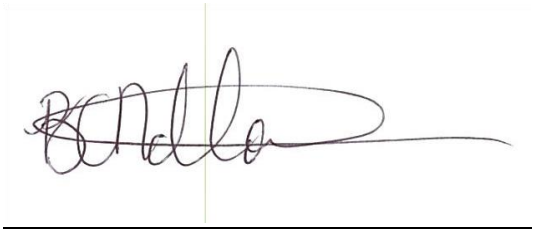
A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Epidemiology (Field Epidemiology) in conjunction with fulfilment of the requirements for the Field Epidemiology training in the South African Field Epidemiology Training Programme.

Johannesburg, March 2020

DECLARATION

I, Miss Babongile Confidence Ndlovu declare that this research report is my unaided work. This dissertation is in partial fulfilment of the Master of Science in Epidemiology (Field Epidemiology) in conjunction with fulfilment of the requirements for the Field Epidemiology training in the South African Field Epidemiology Training Programme. This work has not been submitted before for any degree or examination at any other University.

Signature of candidate



_____ this 20th day of March 2020.

SUPERVISORS, CONTRIBUTIONS AND AFFILIATIONS

Dr Elvira Singh[1, 2]

Primary Field Supervisor: Project conception, Protocol Development, Results Analysis, and Dissertation revision

Dr Mazvita Sengayi-Muchengeti[1, 2]

Secondary Field Supervisor: Project conception, Protocol Development, Results Analysis, and Dissertation revision

Dr Lazarus Kuonza[2, 3]

South African Field Epidemiology Training Program Supervisor: Protocol Development, and Dissertation revision

[1]*National Cancer Registry, National Institute for Communicable Diseases, a Division of the National Health Laboratory Service, Johannesburg, South Africa*

[2]*School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*

[3]*South African Field Epidemiology Training Program, National Institute for Communicable Diseases, a Division of the National Health Laboratory Service, Johannesburg, South Africa*

ABSTRACT

Background: Skin cancer is the most frequently diagnosed malignancy at both global and regional levels. The black population is known to be at a lower risk of developing skin cancer. Despite protection by melanin, skin cancers still occur in black populations. The aim of this study was to identify risk factors associated with skin cancer among black South Africans (SA) presenting at selected tertiary hospitals in the Gauteng Province, 1995-2016.

Methods: The current study used data from the Johannesburg Cancer Study (JCS). JCS recruited adult (18+ years old), consenting, self-defined black SA patients newly diagnosed with cancer and attending public referral hospitals (Chris Hani Baragwanath, Hillbrow and Charlotte Maxeke Johannesburg Academic Hospital) in Johannesburg. Risk factor information on different cancers, including sexual and reproductive behaviour, alcohol use, smoking, sex, urbanicity, etc. were collected. A case control study was then conducted. Cases were those patients with a diagnosis of a skin cancer (non-melanoma skin cancer (NMSC) and/or melanoma skin cancer (MSC)) and controls were those without a cancer diagnosis. The following exposures were assessed; socio-demographic (sex, age, province of birth, rural/urban dweller in the province of birth, province of current residency, rural/urban dweller at current province of residency, and level of education), environmental (type of walls of the house the patient lives in, whether they cook indoors/ outdoors currently and in the past, type of cooking fuel used currently and in the past, and type of warming fuel used currently and in the past), behavioural (smoking status and snuff use), and HIV status. STATA MP version 15 was used to determine proportions of cases by; skin cancer major subtype, demographics, histological spectrum and anatomical site of distribution. A stepwise (backward elimination) logistic regression was done to identify risk factors associated with NMSC and MSC.

Results: Results showed that in this population more NMSCs (n=160) were diagnosed compared to MSCs (n=101). There was equal distribution of NMSCs between males and females. There were more females (60.4%, 61/101) with MSCs compared to males (39.6%, 40/101). The majority of both NMSC and MSC cases were reported in ages 51 to 60 years (27% of all skin cancers). The median age at NMSC diagnosis was the same in both sexes (50 years). The median age at MSC diagnosis was the same in both sexes (mid 50s). The NMSC histological spectrum and anatomical site of distribution showed that there were more squamous cell carcinomas (SCCs) (78/160 in

females, and 72/160 in males) than basal cell carcinoma (BCC) subtypes. The SCC lesions were mostly found on the skin of the head and neck in males (51.4%, 38/72) and on the trunk in females (46.2%, 36/78). MSC was shown to affect the skin of the lower limbs in both males (67.5%, 27/40) and females (59.02%, 36/61). The logistic regression results showed that when age, current urbanicity, type of cooking fuel used currently, smoking, and HIV status were adjusted for; males had 2.04 odds of having NMSC (CI: 1.08-3.84, p=0.028) compared to females. When age, current urbanicity, place of cooking (indoors or outdoors) were adjusted for; males had 2.26 odds of having MSC (CI: 1.19-4.29, p=0.012) compared to females.

Conclusion: The black population was more affected by SCC than by BCC subtype of NMSCs. The SCC lesions were mostly found on the skin of the head and neck in males, and on the skin of trunk in females. Men were found to be at greater odds of being diagnosed with both NMSC and MSC compared to women. Living in a rural area, current smoking and being HIV positive were shown to have positive associations with NMSC outcome. Living in rural area and cooking outdoors were shown to have positive associations with MSC outcome. The current study recommends sun protection initiatives (use of protective clothing and sunscreen) when outdoors. Prevention of HIV infection and/or HIV immunosuppression and quitting smoking might help reduce the risk of NMSC. This study highlights the importance of skin cancer awareness campaigns especially in rural areas because people who live in rural areas had higher odds of both NMSCs and MSC.

ACKNOWLEDGEMENTS

I would like to thank the following programmes, departments, and people for making this work possible. The South African Field Epidemiology Training Programme (SAFETP) for designing a wonderful training programme and by allowing me to partake training under their programme. I thank the programme's financial support for tuition and field work. I acknowledge my SAFETP colleagues for support and advice they have provided throughout the training. I acknowledge Dr Lazarus Kuonza from the SAFETP for providing insightful comments in all my reports. I am grateful for the University of the Witwatersrand's School of Public Health for providing high quality in-class training.

This qualification would not have been possible without the National Cancer Registry (NCR), which was my field placement site during my residency. I thank the supervisors (Dr Mazvita Sengayi-Muchengeti and Dr Elvira Singh) for providing research topics and for being actively involved from the conception of all my projects to the end of each project. I thank these two supervisors for their countless feedback on all my outputs, their teaching style, and their patience. I am grateful for the NCR's financial support covering my monthly allowance and attendance of international conferences to showcase my research. I am grateful for the support that my colleagues from the NCR provided, both academic and emotional support.

I dedicate this dissertation to the South African institutions, which have supported my academic growth; the National Health Laboratory Service's Academic Affairs office for allowing career advancement within the workplace, and the National Research Foundation (NRF) for financial support during my first postgraduate degree, the National Student Financial Aid Scheme (NSFAS) for financial support during my undergraduate degree. I am grateful for the kind of education I received from Ogwini Comprehensive Technical High School. The kind that integrated academia, life skills, and vision. My dreams were incepted at high school level, and my steps directed by passionate teachers who did not only want to see good grades but who were also concerned about my dreams. I specifically acknowledge Dr VS Dlamini for instilling academic excellence and the word of the most high in me.

I will always be thankful for my background circumstances that have always motivated me to be the best that I can be. I thank my late mother Ms Nomusa Gasa for the instruction that she left me with, “to study as much as I can” in order to make a better life for myself. I am grateful for my late grandmother Mrs Mildred MaMkhize Gasa who has supported my decisions regarding my career, and the endless support in the form of prayer and encouragement. I thank God, the most high for letting me live to experience life, education and the goodness of his people.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS AND ACRONYMS

ASIRs Age-Standardized Incidence Rates

BCC Basal Cell Carcinoma

CI Confidence Intervals

CMJAH Charlotte Maxeke Johannesburg Academic Hospital

DNA Deoxyribonucleic Acid

GLOBOCAN Global Cancer Incidence, Mortality and Prevalence

GOF Goodness-of-fit

HIV Human Immunodeficiency Virus

ICD-O3 International Classification of Diseases for Oncology, Version 3

IQR Interquartile Range

JCS Johannesburg Cancer Study

JHB Johannesburg

lr Likelihood ratio test

MSCs Melanoma Skin Cancers

NCR National Cancer Registry

NHLS National Health Laboratory Service

NMSCs Non-Melanoma Skin Cancers

P-value Probability Value

ROC curve Receiver Operating Characteristic Curve

RSA Republic of South Africa

SA South Africa

SCC Squamous Cell Carcinoma

UVR Ultraviolet Rays

WHO World Health Organization

ZAR Zuid-Afrikaanse Rand

CHAPTER ONE - INTRODUCTION

This chapter introduces the subject of skin cancer, its classifications, and epidemiology at global, regional, and national levels. It explores the background of skin cancer in South Africa (SA) and states the problem statement and justification of the study.

1.1 Introduction

Skin cancer is an abnormal and uncontrollable growth of skin cells (1). Skin cancer originates from the cells of the skin epidermis (squamous, basal, or melanocyte cells) and adopts its names from the type of cells in which the cancer arose (2). There are two major subtypes of skin cancer namely non-melanoma skin cancers (NMSCs) and melanoma skin cancers (MSCs) (3,4). NMSC is a result of over-proliferation of keratinocytes and comprise of basal cell carcinoma (BCC), a proliferation of basal cells of the skin and squamous cell carcinoma (SCC); a proliferation of squamous cells of the skin (5). NMSCs are not aggressive and their potential for distal spread is generally very low, however, there is risk of mortality if left untreated (6–8). MSC, also known as cutaneous melanoma is a skin cancer that results from over-proliferation of melanocytes of the skin (9). Generally skin cancers have a better prognosis compared to other cancers, except MSC (10). MSCs are more aggressive, can metastasize quickly and has a higher fatality rate than NMSCs (11). The incidence of both NMSCs and MSC continue to rise annually, in all population groups and skin types worldwide (5).

Accurate global skin cancer incidence trends are difficult to determine as the reporting is not consistent. From the reported cases worldwide, it is shown that skin cancers are the most frequent type of cancers reported (12,13). According to the World Health Organization (WHO) two to three million NMSCs occur globally each year and one in three people diagnosed with cancer has a skin cancer (12,14). Globally, there were more than 232 000 new cases and 55 000 deaths associated with MSC in 2012 (14). The age-standardized incidence rates (ASIRs) of NMSC and MSC are 14 per 100 000 and 4 per 100 000 people respectively, as shown by the Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) 2018 statistics (15). The 2008 world cancer report demonstrated increased rates of BCC by 35% and of SCC by 133% since 1985 (12). ASIRs of skin cancers vary 100-fold between countries worldwide (14). Skin cancer ASIRs are highest in

countries with predominantly Caucasian populations (14). Many conclusions about skin cancers have been drawn from data collected from non-black populations. This study aims to study skin cancers in the context of South Africa (SA), a country with a predominantly black population.

SA is a population of multiracial groups that are classified into four categories namely; Black African (79.2%), White (8.9%), Coloured (8.9%), and Asian (2.5%) according to the 2011 census figures (16). In SA it is the non-Black population groups that have had higher incidences of skin cancers (17,18). A study by Norval *et al*., on incidence of skin cancers in the population groups of SA from 2000-2004 showed that the White population is the most susceptible population group to skin cancer, followed by Coloureds, Asians, then Blacks (19). The ASIRs of NMSCs were reported to be 4.76 per 100,000 in the non-White population and 19.2 per 100,000 in Whites in SA (19). However, it has been shown that skin cancer incidence has been gradually increasing in the black population and is now amongst the top 18 most common cancers in a black population (20).

1.2 Problem Statement

The Black population has been known to be at a lower risk of developing skin cancer due to the higher melanin content in their skin which provides protection against the ultra-violet rays from sunlight, a major risk factor for skin cancer (21,22). However, even when the numbers are still lower than those in non-Black populations, there has been a rise of skin cancer incidence among the Black population as indicated by the SA annual cancer incidence reports (17). The incidence rates of skin cancer are well documented in SA but the risk factors associated with increased incidence among the black population have not been explored and therefore need investigation (19).

1.3 Justification of the study

A high burden of human immunodeficiency virus (HIV) infection in the Black population of South Africa leads to susceptibilities to many diseases (including cancer) due to immunosuppression (4,23–25). In addition, in the antiretroviral era, HIV positive patients live longer and grow older to develop chronic diseases like cancer (4,23–25). Skin cancer is no exception; the SCC subtype of skin cancer has been shown to be associated with HIV infection [OR 2.6, 95% CI (1.4 - 4.9)]

(26). Skin cancer is of public health concern in SA due to the country's high ambient ultraviolet radiation environment and high burden of HIV (18). Understanding skin cancer incidence patterns and aetiology in a Black population, the largest population group in South Africa, is critical for planning, prevention, treatment strategies, and allocation of medical resources (18).

The cost(s) associated with managing skin cancer in SA is sizable; ZAR 92.4 million, in 2015 (18). The cost of managing skin cancers can be reduced by studying the risk factors associated with skin cancer, and implementing prevention measures appropriate to the local population (18).

CHAPTER TWO – LITERATURE REVIEW

This chapter reviews literature on the main risk factors associated with skin cancer and lists other risk factors that have been shown to be associated with skin cancer. The risk factors of skin cancer in SA Black population are a gap in the body of knowledge, which the current study aims to address. This chapter ends with a description of the aims and objectives of the study.

2.1 Background literature analysis and critique

2.1.1 Overview of skin cancer risk factors

Skin cancer results from environmental exposures combined with inherent factors and behaviours (27). Risk factors that have been shown to be associated with skin cancer are; ultraviolet radiation (UVR) mostly through sun exposure (a primary skin cancer risk factor that accounts for more than 80% of skin cancer incidences), geographic location (living near the equator or higher altitudes and living in areas whose ozone layer has been depleted) (9,28,29). Ethnicity, lifestyle behaviours (sunbed use, tobacco smoking, and alcohol drinking), sex, HIV infection, albinism, older age, use of anti-hypertensive drugs (i.e. thiazide diuretics) has shown association with skin cancer in different research studies (2,8,10,13,30,31). Factors like education are associated with health awareness, which in turn determines one's ability to avoid behaviours associated with ill-health (32). Other risk factors that have been shown to be associated with skin cancer development are; many melanocytic nevi during childhood, lightness in complexion, long history of sunburns, light-coloured eyes (blue, green, grey), and light-coloured hair (4,7,18,22–24,33).

2.1.2 Ultraviolet radiation exposure

Exposure to excessive UVR through sun exposure especially during childhood explains most of the skin cancer cases in adulthood (22,30,34). It has been shown that longer duration of exposure to UVR increases the odds of having skin cancer (4,18,23). The Black population have misperceptions about their risk of skin cancer and strongly believe that they are fully protected from the damaging effects of UVR (35). Black skin is known to possess abundant melanin skin pigment which plays a role in protection against skin cancer, mainly via a natural tan (36). However, it has been shown that black skin is not immune against skin damage caused by UVR

exposure (36). Given enough exposure to UVR some DNA damage is observed in black skin, although not as severe as that of a white skin (36). As a protective mechanism it has been recommended that sun exposure should be minimized (both by black and white skinned populations); the use of hats has been encouraged and the use of sunscreen creams to protect one's skin from UVR damaging effects (18,22).

2.1.3 Geographic location and ozone hole

History of exposures is of importance when analyzing data in association studies (27). Geographic location of an individual plays a crucial role in the development of skin cancer (37). Living near the equator especially in childhood through early teenagehood has been shown to be associated with skin cancer development in adulthood (4,7,18,22–24). This is explained by high ambient sunlight exposure experienced by those who live near the equator where the ozone layer is weakening (9,29).

The ozone layer (O_3) absorbs more than 90% of the sun's high frequency ultraviolet light, which is potentially damaging to life on earth (29). Experiments on animals show that UV exposure decreases the immune response to skin cancers, infectious agents and other antigens (29). The weakening of the ozone layer increases penetration of solar UVR and has a negative impact on human health with increased risk of skin cancer and other diseases (34). Light skinned human populations, are at higher risk of developing NMSC (29).

2.1.4 Ethnicity

Skin cancer is most common amongst Caucasians (5). Caucasians have been shown to be the most susceptible population to NMSCs (14). Dark skinned individuals are known to be less likely to develop NMSCs and MSCs, as a result of abundant melanin on the skin (24). Melanin has a protective effect from UVR light exposure, which is a main risk factor for skin cancer (24). Irrespective of the Black population having melanin in abundance, a considerable number of the black people are still affected by skin cancer and this warrants further investigation. South Africa has high levels of solar UVR and year-round exposure to high ambient UVR which are known to be the main risk factors for skin cancer development (10).

2.1.5 Lifestyle behaviours

Lifestyle behaviours such as sunbed use, tobacco use (via smoking or snuff use) and alcohol consumption play a substantial role in the development of skin cancer (38,39). Tobacco and alcohol use has been shown to play a role in carcinogenesis and it is estimated that 25–30% of all cancers in developed countries are tobacco-related (38). Tobacco users are two times more likely to develop skin cancer compared to those who do not use tobacco as shown in the Dutch population study (8). Reducing or eliminating alcohol intake proves to be a prevention strategy that has a large impact on the development of MSC and other cancers (40). Sunbed use, a habit practiced mostly in the northern Europe and the United States is not safe as studies have shown that ultraviolet tanning units may be 10 to 15 times stronger than the actual rays from the sunlight (39). Indoor tanning through sunbed use has negative effects and is associated with skin cancer development (39,41).

2.1.6 Sex

Sex has been shown to be an important determinant of skin cancer susceptibility with sex specific differences according to the type of skin cancer (31). Generally males are more likely to be diagnosed with skin cancer than females (42). Skin cancer is greatly associated with exposure to UVR, and males generally have jobs outside (agricultural jobs, or mining jobs) which exposes them to excess UVR (10). The differences in skin cancer incidence between the two sexes may be a result of health seeking behavioural differences (31). Females are more likely to seek medical help over a suspicious looking lesion than men (31).

2.1.7 Albinism

Albinism is a genetically inherited disorder with a worldwide distribution and is associated with and increased incidence of skin cancer (7,43). Phenotypically it presents with reduced or no melanin in the hair, the skin and the eyes (43). The lack of melanin and exposure to intense UVR increases the risk of developing skin cancer (43). Skin cancer is a major cause of morbidity and mortality in people living with albinism as they develop cancerous lesions at a younger age and suffer from advanced skin cancers later in life (42,43).

2.1.8 Age

In general, age is an important risk factor for skin cancer development, with a higher risk with increasing age (13). Although skin cancers can be diagnosed at any age, it is more frequent in individuals 66 years and older (13).

2.1.9 Thiazide diuretics use

The use of anti-hypertensive drugs such as thiazide diuretics has been shown to be associated with skin cancer susceptibility disorders, although the results are conflicting (33). Thiazide diuretics are recommended as first line antihypertensive agents for all ethnicities and are among the widely prescribed antihypertensive medications worldwide (33). Thiazides have been reported to be photosensitizing agents that may trigger an abnormal skin response to UVR thus increasing the risk of skin cancers (33). The use of thiazide diuretics was associated with an increased risk of SCC, marginal increased risk of BCC, and MSC (33).

2.1.10 Occupational exposure

Occupational exposures also have an impact on disease development, for example individuals working in outdoor occupations are at a greater risk of developing NMSC, as they are likely to be outside for more daylight hours (10). Occupational exposure coupled to geographic location elevates the risk of skin cancers as these individuals are exposed to sunlight when the sun is very hot (during the day) and if it's hot all year round (in higher altitudes) (10). Occupational exposure to industrial creosote, copper, chromium, and arsenic have indicated an elevated risk of skin cancer (44). There is a doubled risk for skin cancer attributed to the combination of exposure to creosote and sunlight (44). In SA it has been shown that occupational skin cancer cases are related to industrial exposures to chemical carcinogens such as polycyclic aromatic hydrocarbons (PAH) and arsenic (45). PAH from shale oil, tar, pitch, raw paraffin, creosote, asphalt, and chimney soot have been associated with risk to skin cancers (45). Workers from coal, aluminium production plants, steel and iron foundries, and diesel plants are at higher risk of skin cancer (45). Arsenic in pesticides also represents a potential skin cancer risk for agriculture workers (45). Occupational exposure to and smelting arsenic (in mining industries) combined with sunlight exposure creates an increased risk of NMSC (45).

2.1.11 HIV infection

It has been shown that immunosuppression through HIV leads to a 3 to 5-fold increased risk of developing NMSC (10). The immunosuppression in people living with HIV was shown to lead to BCC and SCC in a Danish cohort study (46).

Through education and knowledge, skin cancer's biggest risk factor; exposure to excessive sunlight, may be removed/minimized by avoiding direct sunlight exposure or by using sunscreen creams for protection (30).

In the current study we assessed socio-demographic factors (sex, age group, place of residency, and level of education), environmental factors (type of walls of the house the patients live in, type of cooking fuel used, and warming fuel used), behavioural factors (smoking, snuff use, and alcohol consumption), type of occupation, and HIV status. In the current study UVR was not adjusted for in the analysis as we did not have a measure of sunlight exposure (a well-established skin cancer risk factor). However, we do not anticipate that this will cause a problem in the analysis as both controls and cases were assumed to be exposed to the same degree of ultra violet light as they live in the same country, hence exposure to the same intensity of UVR (same latitude and longitude). Other risk factors, as per literature review (such as information on a patient's history of hypertension and it's treatment), employment history and if the patient is living with albinism was not collected in the original study.

2.2 Aim

The aim of this study was to identify risk factors associated with skin cancer among Black South Africans presenting at a tertiary hospital in the Gauteng Province, 1995-2016. This is a secondary analysis of data in patients recruited to the Johannesburg Cancer Study (JCS).

2.3 Objectives

The specific objectives were:

1. To determine the proportion distribution of skin cancers among Black cancer patients in the Johannesburg Cancer Study in the Gauteng Province of South Africa, 1995-2016 by:

skin cancer major subtypes, demographics, histological spectrum and anatomical site of distribution.

2. To identify risk factors associated with non-melanoma skin cancers among Black cancer patients in the Johannesburg Cancer Study
3. To identify risk factors associated with melanoma skin cancers among Black cancer patients in the Johannesburg Cancer Study

CHAPTER THREE - METHODS

This chapter describes the Johannesburg Cancer Study (JCS) in which the current study (secondary data) is nested. The chapter also describes, in detail the methods used in the current study (study design, study setting, study participants, data collection, sample size, data management, variables, data analysis and statistical methods used, and ethical considerations).

3.1 Methods

3.1.1 Study design

The JCS is a case control study conducted from 1995 – 2016. Cases were those patients with a diagnosis of a skin cancer (NMSC and/or MSC) and controls were those with a non-cancer diagnosis. This current study is a secondary data analysis of the data collected by the JCS.

3.1.2 Study setting

The parent study, the JCS, was done in Johannesburg, in three conveniently selected referral hospitals (Chris Hani Baragwanath, Hillbrow and Charlotte Maxeke Johannesburg Academic Hospitals). Johannesburg is a city in the Gauteng Province of SA, with the highest economic activity in the country (47). People from all over SA migrate to Johannesburg for employment, hence the city's population contains a mixture of ethnicities and is therefore a representative of SA as a whole (47).

3.1.3 Study participants

The primary study, the JCS, recruited adult (18+ years old), consenting (see appendix V; JCS informed consent form), self-defined black South African patients who were newly diagnosed with cancer and attending public referral hospitals (Chris Hani Baragwanath, Hillbrow and Charlotte Maxeke Johannesburg Academic Hospitals) for oncology and radiation therapy in Johannesburg (48). The primary study was conducted by the National Cancer Registry (NCR) of SA between 1995 and 2016 (48).

All black patients who were 18 years and older at the time of recruitment that had a diagnosis of skin cancer (NMSC and MSC), were included in the analysis. Skin malignancies that did not form part of the two main skin cancer subtypes (NMSC and MSC) were excluded from the study. Controls were randomly selected from a JCS controls dataset using a SATA command sample n, count. All control observations with non-missing data were considered for selection. Stata was used to select controls using a sampling without replacement method.

3.1.4 Data collection

The JCS, with the aim of collecting socio-demographic and environmental factors associated with cancer, conducted face-to-face interviews, using a paper-based questionnaire (see appendix VI; JCS questionnaire). The questionnaire was administered by qualified nurses to collect risk factor information of different cancers, including sexual and reproductive behaviour, alcohol use, smoking, and other exposures. In addition to risk factor information collection, consenting participants donated blood specimens for evaluation of infectious and genetic risk factors for cancer (48). Data were collected from a total number of 26 263 patients from the years 1995 to 2016. A subset of controls (non-cancer) were recruited using a convenience sample framework, from the cardiology department at CMJAH. The same questionnaire was used to collect the information from these participants. The data was entered into Epi Info and exported and stored in a STATA 15 database (the database is in the custodianship and curatorship of the NCR).

For the current study, three subsets of datasets were extracted from the JCS dataset; a NMSC dataset (n=160), a MSC dataset (n=101), and a controls dataset (n=1130). Random selection of 160 controls for NMSC and 101 controls for MSC was done from a JCS controls dataset and was appended to the NMSC and MSC datasets, respectively.

3.1.5 Study power

In the current study, only power could be calculate as per given number of cases. Forty seven percent of males had an outcome and 28% had no outcome of skin cancer. When the power of two proportions were calculated, a 1:1 case control at 0.05 significance level yielded a power of 70% and 50% for the NMSC and MSC analysis, respectively.

3.1.6 Data management

The dataset (skin cancer records, and controls) for the current study was extracted from the parent JCS database by data managers and provided to the researcher over secure electronic channels. Data management, cleaning and analysis was done using STATA MP statistical software (version 15). Each patient had a unique study identifier therefore patient identifiers were not used in this study. Cancer coding consistency was evaluated using the International Classification of Diseases for Oncology, version 3 (ICD-O3) book (49). Observations which had an ICD-O3 topography code for skin and ICD-O3 morphology codes for NMSCs and MSCs were kept for this analysis.

New variables were created namely; histological spectrum and anatomical site. The histological spectrum variable (created from the ICD-O3 m code) differentiated the two main types of NMSCs (SCC, and BCC) and MSC. The anatomical site variable (created from the ICD-O-3 t code) marked records according to their site of origin; i.e. the skin of the head and neck, skin of the upper limbs, skin of lower limbs, skin of the trunk, and overlapping skin sites.

3.1.7 Variables

3.1.7.1 Outcome variable

A binary outcome variable was created (0-no cancer, 1-skin cancer) in both the NMSC and MSC datasets.

3.1.7.2 Exposure variables

The exposure variables of interest that were analysed in this study were; socio-demographic variables (sex, age, province of birth, rural/urban dweller in the province of birth, province of current residency, rural/urban dweller at current province of residency, and level of education), environmental variables (type of walls of the house the patient lives in, whether they cook indoors/ outdoors currently and in the past, type of cooking fuel used currently and in the past, and type of warming fuel used currently and in the past), behavioural variables (smoking status and snuff use), and HIV status.

3.1.8 Data analysis and statistical methods

Proportion percentages of cases were described according to the two major skin cancer groups (NMSC and MSC) and stratified by sex. The analysis defined proportion percentages between males and females by number of cases, median age, and 10-year gap age-grouping. The NMSCs were further described by histological spectrum (BCC and SCC) and anatomical site (skin of; head and neck, upper limbs, lower limbs, and trunk). We then did a stepwise (backward elimination) regression analysis to identify factors associated with each skin cancer subtype.

3.1.9 Univariable analysis

On our unadjusted model we regressed sex (primary exposure) to the outcome of skin cancer. Univariable logistic regression was done to test associations of individual factors with the outcome of skin cancer (NMSC and MSC separately). Testing of individual associations of socio-demographic variables (age, province of birth, rural/urban of province at birth, province of current residency, rural/urban dweller at current residency, and level of education), environmental variables (type of walls of the house the patient lives in, whether cooking is done indoors or outdoors, type of cooking fuel used currently and in the past, and type of warming fuel used currently and in the past), behavioural variables (smoking status and snuff use), and HIV status with the outcome (NMSC and/or MSC) was done.

3.2.0 Model building

This was an exploratory study of skin cancer risk factors in a Black population of South Africa. We used both data-driven and biological plausibility approaches to build our regression model.

3.2.1 Stepwise regression analysis

All variables that were hypothesized to have an association with skin cancer (NMSC or MSC) outcome were included in a stepwise regression model. We fitted separate multivariable models for NMSC and MSC. We used the STATA command *stepwise* to conduct stepwise backward elimination at a 0.1 significance level of removal from the model. We used the *lr* option so that likelihood ratio tests were used to compare models in the stepwise regression. Factors that had no

significant associations with the outcome were automatically removed from the model by the stepwise regression.

3.2.3 Multivariable analysis, model stability, and model testing

The multivariable model included variables that were kept from backward elimination from stepwise regression. Variables which were excluded from the model due to insignificant p-values from the stepwise regression, but with biological plausibility were included in the final model, regardless of them being insignificant e.g. age and place of cooking (indoors or outdoors). Age tells us more about the duration of exposure to the skin cancer risk factors. The place of cooking is used as a proxy to measure sun exposure, which is a well-established skin cancer risk factor.

For model stability, we excluded variables that had insufficient events for individual categories (e.g. province of residence in the past and at present). We combined gas and paraffin under cooking fuels used because gas use did not have enough events and could be grouped together with paraffin as combustible materials. We removed variables that showed collinearity with other variables e.g. we kept fuel used for cooking and excluded fuel used for warming. These two variables had the same responses as it is likely that the same kind of cooking fuel will be used as a warming fuel as well. Exposure-wise, it is likely that a person is exposed to cooking fuel more than they are exposed to warming fuel because in SA winter only lasts for a few months but cooking is done throughout the year. The latter also played a role in achieving a parsimonious model that explains the relationship between sex and skin cancer, adjusting for all the other variables that were kept in stepwise regression. We kept variables that have been shown to have an association with skin cancer in literature, i.e. age, and we used age as a continuous variable as opposed to categorized in order to have a less strained model. The first model improvements were tested using the likelihood ratio test to identify the best fit model. Post-regression tests were done to assess the model's goodness-of-fit (GOF) and the area under the ROC curve on the final models (for both NMSC and MSC regression models).

3.3 Ethical considerations

Approval to conduct the study was obtained from the Human Research Ethics Committee (Medical) of the University of Witwatersrand, clearance certificate number: M181191 (see appendix I). Permission was obtained from the respective gatekeepers of the primary dataset (appendix III). The primary JCS study also has the approval of the ethics committee, clearance certificate number: M1606103 (see appendix IV). Anonymized data were obtained, and they were kept in a password-protected NHLS computer to ensure confidentiality of participants.

CHAPTER FOUR - RESULTS

This chapter describes the demographic characteristics of NMSC and MSC cases within the JCS in South Africa between 1995 and 2016. The histological spectrum and anatomical site of the cases, stratified by sex is also shown. The chapter concludes by showing the results of the logistic regression of NMSCs and MSCs with respect to the hypothesized risk factors. Both univariable and multivariable logistic regression results are presented.

4.1 Results

4.1.1 Demographics

There were 160 NMSC cases in the study, of which 75 (46.9%) were males and 85 (53.1%) were females. The median age in males was 51 years and in females was 46 years. The NMSC cases were distributed across 10-year age groups and most cases were recorded in age group 51-60 years (27.5%, 44/160). There were 101 MSC cases in the study, of which 40 (39.6%) were males and 61 (60.4%) were females. The median age in males was 55 years and in females was 56 years. Most MSC cases were recorded in age group 51-60 years (27.7%, 28/101), Table 1.

Table 1: Case distribution of NMSC and MSC cases in the Johannesburg Cancer Study, 1995-2016

	NON-MELANOMA SKIN CANCER			**MELANOMA SKIN CANCER**		
	All	**Males**	**Females**	**All**	**Males**	**Females**
N (row %)	160 (100%)	75 (46.9%)	85 (53.1%)	101 (100%)	40 (39.6%)	61 (60.4%)
Age median in years (IQR)	49 (38-57)	51 (41-59)	46 (36-56)	56 (48-68)	55 (49-68)	56 (47-68)
Age-groups, n (col %)						
18-30	17 (10.6%)	4 (5.3%)	13 (15.3%)	2 (2.0%)	1 (2.5%)	1 (1.64%)
31-40	33 (20.6%)	14 (18.7%)	19 (22.4%)	10 (10.0%)	3 (7.5%)	7 (11.5%)
41-50	40 (25.0%)	19 (25.3%)	21 (24.7%)	21 (20.8%)	9 (22.5%)	12 (19.7%)
51-60	44 (27.5%)	26 (34.7%)	18 (21.2%)	28 (27.7%)	12 (30.0%)	16 (26.3%)
61-70	21 (13.1%)	10 (13.3%)	11 (12.9%)	17 (16.8%)	7 (17.5%)	10 (16.4%)
71-80	3 (1.9%)	1 (1.3%)	2 (2.4%)	17 (16.8%)	5 (12.5%)	12 (19.7%)
81+	2 (1.3%)	1 (1.3%)	1 (1.2%)	6 (5.9%)	3 (7.5%)	3 (4.9%)

4.1.2 Histological spectrum and anatomical site

There were more SCCs in both females (n=78) and males (n=72) compared to BCC. The distribution of SCC in females showed that most cases were recorded on the skin of the head and neck, 30/78 (38.46%) and skin of trunk, 36/78 (46.15%). In males 37/72 (51.39%) SCCs were recorded on the skin of the head and neck and 13/72 (18.06%) on the skin of the trunk. The MSC was recorded the most commonly on the skin of lower limbs in both females and males, 36/61 (59.02%) and 27/40 (67.50%), respectively, (Figure 1).

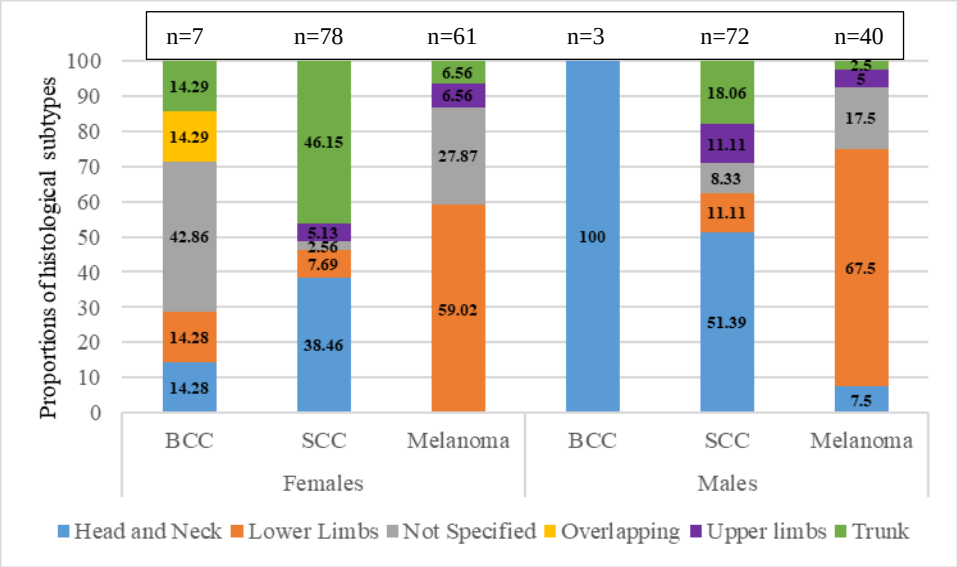


Figure 1: Histological spectrum and anatomical site of distribution of skin cancers in the Johannesburg Cancer Study, 1995-2016. BCC – Basal cell carcinoma, SCC – Squamous cell carcinoma.

4.1.3 Risk factor analysis

4.1.3.1 Non-melanoma skin cancer

Univariable results

In univariable analysis males were shown to have 2.56 odds of having NMSC compared to females (CI: 1.60-4.10, p<0.001), (Table 2). This model (with only sex) explained 3.56% of the variation observed in the outcome, (Table 2). Individual regressions of; province of birth (Gauteng, Mpumalanga, North West, and Free State), being born in a rural area, residing in (Gauteng, North West, and Free State), living in a rural area, a history of using paraffin or gas as a warming fuel,

current smoking and being HIV positive showed significantly higher odds of association with NMSC at a p-value of ≤0.05, (Table 2). Individual regression of current snuff use showed negative association with NMSC, (Table 2). No significant relationship was found between; age, level of education, type of house walls, place of cooking (current or in the past), cooking fuel used (currently or in the past), and type of warming fuel used in the past with NMSC, (Table 2).

Multivariable results

When sex, age, province of birth, being born in a rural area/ urban area, province of residence, living in a rural/ urban area, type of walls of the house the participant lives in, whether they cook indoors or outdoors currently or in the past, the type of cooking fuel they used in the past or currently, the type of warming fuel they used in the past or currently, smoking, snuff use, and HIV status were regressed on stepwise backward elimination, the following variables were dropped from the model due to insignificant association(s) with NMSC outcome (p-value >0.1); type of warming and cooking fuels used in the past, whether cooking was done outdoors or indoors currently or in the past, province of birth, urbanicity of place of birth, snuff use, age, and level of education. In the final model we retained age, place of cooking (indoors or outdoors) for biological plausibility and as a sunlight exposure proxy. We removed province of residence because most cells had fewer observations and others had empty observations. We also removed the type of walls of the house the participant lives in because there is no biological plausibility for this association. We removed warming fuel because of collinearity with cooking fuel.

The final model showed that when age, current urbanicity, type of cooking fuel used currently, smoking, and HIV status were adjusted for; males had 2.04 odds of having NMSC (CI: 1.08-3.84, p=0.028) (Table 2). This model explained 11.33% of the variation observed in NMSC outcome, as opposed to the univariable analysis (with only sex) which only explained 3.56% of the variation. Significant association of smoking and HIV infection with NMSC were found; current smokers (2.65, CI: 1.24-5.64, p-value 0.012) and HIV positive (2.00 odds, CI:1.09-3.53, p-value 0.024). Marginal significance of urbanicity and cooking fuel with NMSC was observed; rural dwellers (4.5 odds, CI: 1.58-13.06, p-value 0.005) and using wood as cooking fuel showed protective effects to NMSC (0.16 odds, CI:0.02-1.13, p-value 0.065). Age was kept in the final model for face validity, as it is known as a risk factor for cancer and should always be adjusted for in models.

Table 2: Univariable and multivariable logistic regression of non-melanoma skin cancer risk factors in black South Africans, JCS 1995-2014.

	Univariable logistic regression (p≤0.25)			**Multivariable logistic regression analysis**		
	Unadjusted Odds Ratios	**95% Confidence Intervals**	**P-values**	**Adjusted Odds Ratios**	**95% Confidence Intervals**	**P-values**
SOCIO-DEMOGRAPHIC VARIABLES	n=320, R^2=0.0356, p=0.000			n=293, R^2=0.1133, p=0.000		
Gender (n=320)						
Female (ref)	1			1		
Male	2.56	1.60-4.10	0.000	2.04	1.08-3.84	0.028
Age (n=320)	0.98	0.97-1.00	0.040	0.99	0.97-1.01	0.591
Province of birth (n=317)						
Soweto (ref)	1					
Rest of JHB	1.24	0.47-3.31	0.663			
Rest of Gauteng	3.50	1.66-7.37	0.001			
Limpopo Province	1.89	0.74-4.86	0.184			
Mpumalanga	4.42	1.44-13.55	0.009			
North West	2.95	1.17-7.43	0.022			
Free State	5.65	2.20-14.49	0.000			
Eastern Cape	1.66	0.60-4.60	0.331			
Northen Cape	3.32	0.51-21.50	0.209			
KwaZulu Natal	1.33	0.49-3.56	0.575			
Outside RSA	4.42	1.33-14.72	0.015			
Urbanicity of place of birth (n=316)						
Urban (ref)	1					
Rural	1.63	1.04-2.54	0.03			
Province currently living in (n=306)						
Soweto (ref)	1					
Rest of JHB	0.87	0.41-1.87	0.723			
Rest of Gauteng	3.14	1.82-5.44	0.000			
Limpopo Province	2.53	0.76-8.48	0.131			
Mpumalanga	-	-	-			
North West	4.34	1.43-13.17	0.009			
Free State	12.67	1.51-106.47	0.019			
Eastern Cape	1.81	0.25-13.32	0.560			
Northen Cape	-	-	-			
KwaZulu Natal	3.62	0.32-41.10	0.300			
Outside RSA	-	-	-			
Rural/Urban dweller currently (n=316)						
Urban (ref)	1			1		
Rural	2.70	1.25-5.84	0.011	4.5	1.58-13.06	0.005
Level of education (n=313)						
Tertiary (ref)	1					
None	1.84	0.51-6.71	0.36			
Primary	1.58	0.47-5.26	0.46			
Secondary	1.21	0.37-4.01	0.75			
ENVIRONMENTAL VARIABLES						
Type of walls of the house the patient lives in (n=315)						
Brick/concrete (ref)	1					

Tin	0.78	0.43-1.41	0.405			
Wood	1.00	-	-			
Mud/clay	0.63	0.10-3.81	0.611			
other	0.47	0.04-5.24	0.539			
Place of cooking currently (n=313)						
Inside (ref)	1			1		
Outside	5.10	0.59-44.15	0.139	7.42	0.50-110.90	0.146
Type of cooking fuel used currently (n=316)						
Electricity (ref)	1			1		
Wood	1.46	0.45-4.73	0.528	0.16	0.02-1.13	0.065
Coal	0.91	0.43-1.95	0.814	0.69	0.28-1.71	0.422
Paraffin_Gas	1.53	0.76-3.09	0.236	0.92	0.41-2.09	0.845
Type of warming fuel used currently (n=308)						
Electricity (ref)	1					
Wood	1.79	0.65-4.87	0.258			
Coal	1.55	0.82-2.93	0.179			
Paraffin_Gas	2.25	0.99-5.11	0.05			
Place of cooking in the past (n=315)						
Inside (ref)	1					
Outside	1.49	0.71-3.138	0.29			
Type of cooking fuel used in the past (n=315)						
Electricity (ref)	1					
Wood	1.67	0.84-3.31	0.144			
Coal	0.65	0.36-1.18	0.157			
Paraffin-Gas	2.01	0.72-5.61	0.183			
Type of warming fuel used in the past (n=308)						
Electricity (ref)	1					
Wood	1.71	0.83-3.52	0.146			
Coal	0.68	0.36-1.28	0.233			
Paraffin_Gas	2.50	0.78-8.04	0.124			
BEHAVIOURAL VARIABLES						
Smoking (n=316)						
Never smoked (ref)	1			1		
Smoked in the past	1.60	0.91-2.81	0.103	1.73	0.88-3.39	0.113
Current smoker	3.08	1.74-5.46	0.000	2.65	1.24-5.64	0.012
Snuff use (n=315)						
Never used (ref)	1					
Used in the past	0.67	0.32-1.40	0.287			
Current user	0.34	0.15-0.76	0.008			
HIV STATUS (n=300)						
Negative (ref)	1					
Positive	1.72	1.06-2.78	0.028	2.00	1.09-3.53	0.024

Post-regression test results

Goodness-of-fit test results: Age as a continuous variable (p-value=0.2870), Age as a categorical variable (p-value=0.0634).
Area under the ROC curve results: Age as a continuous variable (p-value=0. 0.7277), Age as a categorical variable (p-value=0.7539).

4.1.3.2 Melanoma skin cancer

Univariable results

In univariable analysis males were shown to have 1.99 odds of having MSC compared to females (CI: 1.09-3.64, p=0.025), (Table 3). This model (with only sex) explained 1.83% of the variation observed in the outcome, (Table 3). Individual regressions of; province of birth (Gauteng, Limpopo, North West, Free State, and Eastern Cape), being born in a rural area, residing in (Gauteng and Limpopo Provinces), living in a rural area, using wood and coal as a cooking fuel, using wood, coal, paraffin or gas as a warming fuel, a history of cooking outdoors, history of using wood both as a cooking and a warming fuel showed significantly higher odds of association with MSC at a p-value of ≤0.05, (Table 3). Being HIV positive showed negative association with MSC, (Table 3). No significant relationship was found between; age, level of education, type of house walls, current place of cooking, smoking, and snuff use with MSC, (Table 3).

Multivariable results

When sex, age, province of birth, being born in a rural/ urban area, province of residency, living in a rural/ urban area, type of walls of the house the participant lives in, whether they cook indoors or outdoors currently or in the past, the type of cooking fuel they used in the past or currently, the type of warming fuel they used in the past or currently, smoking, snuff use, and HIV status were regressed on stepwise backward elimination, the following variables were dropped from the model due to insignificant association(s) with MSC outcome (p-value >0.1); type of warming and cooking fuels used in the past, type of cooking fuel used currently, whether cooking was done outdoors or indoors currently or in the past, province of birth, urbanicity of place of birth, snuff use, level of education, HIV status and smoking status. In the final model we retained place of cooking (indoors or outdoors) for biological plausibility and as a sun exposure proxy. We removed province of residency because most cells had fewer observations and others had empty observations. We also removed the type of walls of the house the participant lives in because there was no biological plausibility of this variable with skin cancer risk. We removed warming fuel because of collinearity with cooking fuel.

The final model showed that when age, current urbanicity, place of cooking (indoors or outdoors) were adjusted for; males had 2.26 odds of having MSC (CI: 1.19-4.29, p=0.012) (Table 3). This

model explained 8.90% of the variation observed in MSC outcome, as opposed to the univariable analysis (with only sex) which only explained 1.83% of the variation, (Table 3). Significant association of living in rural areas was found; rural dwellers (OR = 2.88, CI: 1.01-8.18, p-value 0.048). Age was kept in the final model for face validity, as it is known as a risk factor for cancer and should always be adjusted for in models. Place of cooking was kept in the model because it served as a proxy for sun exposure.

Table 3: Univariable and multivariable logistic regression of melanoma skin cancer risk factors in black South Africans, JCS 1995-2014.

	Univariable logistic regression (p≤0.25)			**Multivariable logistic regression analysis**		
	Unadjusted Odds Ratios	**95% Confidence Intervals**	**P-values**	**Adjusted Odds Ratios**	**95% Confidence Intervals**	**P-values**
SOCIO-DEMOGRAPHIC VARIABLES	n=202, R^2=0.0183, p=0.023			n=201, R^2=0.0890, p=0.000		
Gender (n=165)						
Female (ref)	1			1		
Male	1.99	1.09-3.64	0.025	2.26	1.19-4.29	0.012
Age (n=202)	1.03	1.01-1.06	0.001	1.04	1.02-1.06	0.001
Province of birth (n=201)						
Soweto (ref)	1					
Rest of JHB	1.79	0.48-6.73	0.389			
Rest of Gauteng	3.63	1.33-9.92	0.012			
Limpopo Province	5.57	1.94-15.97	0.001			
Mpumalanga	3.22	0.76-13.71	0.113			
North West	4.30	1.18-15.70	0.027			
Free State	7.09	1.94-25.88	0.003			
Eastern Cape	6.44	1.18-22.11	0.003			
Northen Cape	3.22	0.18-56.88	0.424			
KwaZulu Natal	1.61	0.39-6.27	0.509			
Outside RSA	7.25	1.80-29.26	0.005			
Urbanicity of place of birth (n=201)						
Urban (ref)	1					
Rural	2.82	1.59-5.00	0.000			
Province of current residency (n=192)						
Soweto (ref)	1					
Rest of JHB	1.76	0.71-4.39	0.224			
Rest of Gauteng	4.32	2.12-8.84	0.000			
Limpopo Province	3.53	0.90-13.86	0.071			
Mpumalanga	-	-	-			
North West	2.35	0.53-10.34	0.258			
Free State	4.70	0.40-54.84	0.217			
Eastern Cape	3.53	0.55-22.74	0.185			
Northen Cape	-	-	-			
KwaZulu Natal	-	-	-			
Outside RSA	-	-	-			
Rural/Urban dweller at current residency (n=201)						
Urban (ref)	1			1		
Rural	3.08	1.23-7.69	0.016	2.88	1.01-8.18	0.048
Level of education (n=201)						
Tertiary (ref)	1					
None	1.92	0.38-9.65	0.427			
Primary	2.07	0.46-9.39	0.346			
Secondary	1.48	0.34-6.52	0.606			
ENVIRONMENTAL VARIABLES						
Type of walls of the house the patient lives in (n=200)						
Brick/concrete (ref)	1					

Tin	1.47	0.65-3.36	0.358			
Wood	-	-	-			
Mud/clay	0.34	0.03-3.31	0.351			
other	-	-	-			
Place of cooking currently (n=201)						
Inside (ref)	1			1		
Outside	3.03	0.31-29.64	0.341	1.42	0.12-17.41	1.784
Type of cooking fuel used currently (n=200)						
Electricity (ref)	1					
Wood	4.15	1.10-15.69	0.036			
Coal	2.74	0.91-8.27	0.073			
Paraffin_Gas	2.08	0.71-6.00	0.177			
Type of warming fuel used currently (n=193)						
Electricity (ref)	1					
Wood	3.13	1.03-9.49	0.044			
Coal	2.84	1.19-6.78	0.018			
Paraffin_Gas	4.26	1.11-16.44	0.035			
Place of cooking in the past (n=201)						
Inside (ref)	1					
Outside	2.50	0.98-6.37	0.055			
Type of cooking fuel used in the past (n=200)						
Electricity (ref)	1					
Wood	2.86	1.22-6.70	0.016			
Coal	0.86	0.43-1.75	0.681			
Paraffin_Gas	0.45	0.08-2.61	0.378			
Type of warming fuel used in the past (n=200)						
Electricity (ref)	1					
Wood	3.50	1.41-8.67	0.007			
Coal	1.14	0.53-2.45	0.731			
Paraffin_Gas	0.35	0.04-3.45	0.369			
BEHAVIOURAL VARIABLES						
Smoking (n=200)						
Never smoked (ref)	1					
Smoked in the past	0.68	0.31-1.50	0.340			
Current smoker	1.00	0.47-2.14	0.996			
Snuff use (n=201)						
Never used (ref)	1					
Used in the past	0.61	0.23-1.66	0.336			
Current user	1.12	0.49-2.58	0.785			
HIV STATUS (n=192)						
Negative (ref)	1					
Positive	0.50	0.26-0.94	0.032			

Post-regression test results

Goodness-of-fit results: Age as a continuous variable: group 8 (p-value=0.8414), group 10 (p-value=0.5317), group 12 (p-value=0.9257). Age as a categorical variable: group 8 (p-value=0.9180), group 10 (p-value= 0.8551), group 12 (p-value= 0.9920).

Area under the ROC curve results: Age as a continuous variable (p-value=0.6985), Age as a categorical variable: (p-value=0.7105).

CHAPTER FIVE – DISCUSSION

This chapter discusses the results of the study in light of other study findings internationally and nationally. The chapter concludes by discussing strengths and limitations of the study.

5.1 Discussion

The results of this risk factor study of skin cancers in a black population of South Africa, showed that more NMSCs were diagnosed compared to MSCs. The majority of NMSC cases were reported in ages 51 to 60 years. There were more females with MSC compared to males, and the median age at diagnosis was the same in both sexes (mid 50s). The histological spectrum and the distribution of anatomical sites showed that there were more SCC than BCC subtypes of NMSCs, and the SCC lesions were mostly found on the skin of the trunk in females and on the skin of head and neck in males. MSC was shown to affect the skin of the lower limbs in both males and females. The risk factors explored for NMSC showed that males were 2.04 times more likely to develop NMSC. Smoking (current) and a positive HIV status were positively associated with NMSC. Males were 2.26 times more likely to develop MSC and being a rural dweller was positively associated with MSC.

Findings from this study are consistent with the world cancer report statistics that NMSCs account for the majority of skin cancers reported (14). Findings from the current study are consistent with the age at which NMSCs are mostly reported. NMSCs are frequently reported in ages of mid-60, as reported by the world cancer report consolidating all NMSC data available worldwide (38). Generally, males are diagnosed with NMSCs more often than females (8,31,38). However, in the current study more females were diagnosed with NMSCs compared to males. The differences in reported numbers among the two sexes may be a result of health seeking behavioral differences between the two sexes (31). It has been shown that females are more likely to seek medical help over a suspicious looking lesion on the skin than males (31). It was also noted that more than 30% of NMSC cases occurred in the younger age group (less than 40 years). Females, in particular, were diagnosed with NMSC at a younger age than men. This suggests a different predisposition to risk between different sexes.

The skin cancer subtype that was reported more frequently in this study population was SCC, consistent with literature that the black population is mostly affected by SCC (12,21,50). The distribution of histological subtypes of NMSC in the SA population shows that BCC is the most abundant subtype, followed by SCC (5,51). This pattern is due to the overwhelming numbers of BCC diagnosed in the Caucasian population in South Africa. However when population group specific analysis is conducted, SCC is leading skin cancer in the Black population, followed by BCC (19). The differences in NMSC histological subtypes distribution suggest different risk factors among different population groups.

A risk factor for SCC in black population is hypothesized to be immunosuppression resulting from HIV infection (10). SA has one of the world's largest HIV epidemics and the black population is the most affected population (10). A rise of SCC incidence in the black population of SA was observed after the beginning of the HIV epidemic (10). Shortly after the introduction of anti-retroviral treatment, a significant decline of SCC incidence was seen in SA and this is consistent with the theory that relates SCC to immunosuppression resulting from HIV infection (10).

Skin cancer has been known to develop on areas of the skin that are exposed to sunlight as a result of UVR exposure (28,30). This phenomenon is explained by a lack of melanin in non-black populations which then predisposes them to skin injury from UVR exposure, increasing the risk of skin cancer (22). This study showed that the skin of the head and neck and trunk are more susceptible to NMSC in this population (Black population). The body area that is normally covered (trunk) and not normally exposed to the sun is susceptible to NMSC especially in females. These findings show that other than the main risk factor (sun UVR exposure), there may be other risk factors associated with skin cancer in the black population.

Skin cancer risk factors have been understudied in the black population since this population is known to have abundant melanin which protects from undesirable effects of sun exposure (main source of UVR) (24). Consistent with the world cancer report statistics, the incidence of skin cancer is rising in SA, a multi-racial population which is predominated by a black sub-population (14,16,19,38). Aiming to close this gap, the current study explored risk factors that could be associated with two main subtypes of skin cancer.

Being male was shown to result in double the odds of having skin cancer for both NMSC and MSC. A 2-fold higher NMSC odds in males re-affirms that males are more susceptible to NMSCs compared to females as supported by other studies in other countries (8,31). Sex differences exist in many physiological conditions and can be explained by various theories (31). Given sun exposure as a primary risk factor for NMSC susceptibility, the high incidence seen in males can be explained by the nature of jobs done usually done by men (outdoor jobs) and by the behaviour during childhood (spending more time outdoors) which explains most of exposure to risk (23,52). The black SA economy relies on agricultural and mining activities, directly translating to the majority of black men working outdoors (10).

In this study, a positive association of NMSC with smoking (current), and a positive HIV status was seen. In SA, smoking has been associated with NMSC, as shown in literature (8,34,53). It has been shown that a current smoker, and a person who has a history of smoking have increased odds of being diagnosed with SCC (8). Our findings are consistent with literature on association between smoking and NMSC. On univariable analysis it was shown that using wood increases the odds of NMSC, but on multivariable analysis the association was not significant. In China, wood impregnators have been shown to likely develop skin cancer (44). Upon burning, wood compounds can be absorbed by the skin and cause clogging which then result in inflammation, and cancer (54).

In univariable analyses it was also shown that wood, coal, paraffin and gas (as either a cooking fuel or a warming fuel) increases the odds of MSC, however in multivariable analyses the association diminished. Literature has shown that industrial workers with paraffin exposure are likely to develop skin cancer (45,55,56). There is a debate on different forms of paraffin and different effects upon exposure, some forms being good for the skin and some bad (55).

5.2 Strengths of the study

The current study addresses the existing gap in knowledge (that of skin cancer risk factors in a Black population). Even though the study participants were recruited only from one study site (limiting the generalizability of findings to SA black population), Johannesburg population is essentially a mixture of all SA provinces. Johannesburg is a central hub of economic activity in

SA (47). People from all SA provinces migrate to Johannesburg for economic advancement, and for medical treatment; hence, this sample is a good representation of the Black SA population. Our findings were consistent with existing literature on the association between NMSC and smoking, and HIV. New associations was also found; using coal as a cooking and a warming fuel, although not significant in the adjusted model (warranting further investigation).

5.3 Limitations of the study

This is a secondary data analysis and therefore the study may not have collected all risk factor information relating to skin cancer. In the current study, UVR was not adjusted for in the analysis, as we did not have a measure of sun exposure (a well-established skin cancer risk factor). However, we did not anticipate that this will cause a problem in the analysis as both controls and cases were assumed to be exposed to the same degree of ultra violet light as they live in the same country, hence exposure to the same intensity of UVR (same latitude and longitude). Other risk factors, as per literature review (such as information on a patient's history of hypertension and it's treatment), employment history and if the patient is living with albinism was not collected in the original study. The original study's aim was to collect major risk factors for all cancers. The conception of the original study did not zoom in to skin cancer risk factors.

The selection of participants in the current study may have underestimated ratio of cases. We had very few BCC cases, as most of the BCC cases are referred to and excised in dermatology departments rather than radiation or medical oncology (where the participants of this study were recruited from), thus there is a bias in the parent study in terms of selection of cases. The comparisons of the cases to the controls might have been done conveniently, as the cases were selected from an oncology department within the hospital, whereas the controls were selected conveniently from a cardiology department at the hospital. There is a chance that these two groups are of different origin and had different exposures. However, the same questionnaire was used in both cases and controls to collect risk factor information.

The incidence of skin cancer in a black population is generally minimal, therefore the power of our study was affected (power of; 70% and 50% for the NMSC and MSC analysis, respectively). However, the sample size was acceptable on the regression analysis and positive associations were

found. Also we could not use the information acquired from data by province because this variable was poorly populated (only Gauteng and the other northern provinces of the country were well-populated). Interpreting high odds of skin cancers from these provinces would be an artefact of data distribution. The study is a case control study; therefore recall bias may have been an issue. Remembering fine details regarding exposures of interest may have been affected.

The goodness-of-fit was unsatisfactory and results of this analysis should be interpreted with caution. The post-regression model did not reach its maximum potential in explaining the outcome using the exposures tested in this analysis. Therefore care should be taken not to generalize these findings to the entire population due to sample selection bias, as the ratios of cases found in the radiology and oncology units are by chance.

CHAPTER SIX – CONCLUSION

This chapter concludes the study. Recommendations based on results are made in order to prevent skin cancer. Recommendations based on study limitations are made, in order to conduct studies that will yield more accurate results.

6.1 Conclusion

Over the years, the incidence of NMSC is increasing in the general population of SA. NMSCs remain the most diagnosed skin malignancy, consistent with global statistics (14). Although fatality rates are low, NMSCs increase morbidity in the population and result in unnecessary budget expenditure for their management (18). The primary risk factor of skin cancer is well established (the UVR exposure) and it greatly affects the non-black population. The unexplained risk in black population has been show in this study as; smoking, rural dwelling and HIV positive status for NMSC and being a rural dweller for MSC.

6.2 Recommendations

As a primary recommendation, people should minimize time spent in direct sunlight and protect their heads by wearing hats and using umbrellas when outdoors. Sunscreen using habits must be reinforced and must be applied in all body sites (including the head especially in balded individuals). Provision of appropriate personal protective clothing and sunscreen by employers for their workers who do outdoor work should be considered. These will prevent exposure to the well explained skin cancer risk factor that is responsible for 80% of skin cancer incidences (10). Secondary recommendations includes; prevention of HIV exposure and/or immunosuppression (since it increases the odds of skin cancer), quitting smoking and/or not starting smoking. Rural dwellers should be made aware of the high risk they have of skin cancers, so that they take precautionary measures mentioned above. In addition, further research is required on combustible fuels and skin cancer development.

6.3 Further opportunities for research

1. We recommend a case control study with enough participants, so as to increase the study power to 80% +.
2. We recommend a primary case control study, specific to skin cancer that will collect all risk factor variables associated with skin cancer.
3. We recommend occupational studies for outdoor workers.
4. We recommend expanding on research studies on coal exposure (or combustible fuels in general) and skin cancer development.
5. We recommend a cohort study, in order to follow participants in real time so that exposures can be measured accurately and therefore to infer causality.

CHAPTER SEVEN – REFERENCES

This chapter lists the sources (research articles, reviews, websites, and reports) that were used for literature synthesis in the current study. Mendeley reference manager (Vancouver style) was used for referencing this document.

7.1 References

1. Health effects of UV radiation [Internet]. World Health Organization; 2017. Available from: http://www.who.int/uv/health/uv_health2/en/index1.html
2. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol. 2012;166(5):1069–80.
3. Erb P, Ji J, Kump E, Mielgo A, Wernii M. Apoptosis and Pathogenesis of Melanoma and Nonmelanoma Skin Cancer. In: 284 Sunlitght, Vitamin D and Skin Cancer. 2008. p. 283–4.
4. Gordon R. Skin Cancer: An Overview of Epidemiology and Risk Factors. Semin Oncol Nurs. 2013;29(3):160–9.
5. Griffin LL, Ali FR, Lear JT. Non-melanoma skin cancer. Clin Med. 2016;16(1):62–5.
6. Oberyszyn TM. Non-melanoma skin cancer: Importance of gender, immunosuppressive status and vitamin D. Cancer Lett. 2008;261:127–36.
7. Chen A, Fu J, Grekin R, Margolis L. Cancer of the skin [Internet]. Science Direct. p. 1439. Available from: https://clinicalgatecom/cancer-of-the-skin-2/
8. De Hertog SAE, Wensveen CAH, Bastiaens MT, Kielich CJ, Berkhout MJP, Westendorp RGJ, et al. Relation Between Smoking and Skin Cancer. J Clin Oncol. 2001;19(1):231–8.
9. Rippey JJ, Rippey E. Epidemiology of malignant melanoma of the skin in South Africa. Vol. 65, SA Medical Journal. 1984.
10. York K, Dlova NC, Wright CY, Khumalo NP, Kellett PE, Kassanjee R, et al. Primary cutaneous malignancies in the Northern Cape Province of South Africa: A retrospective

histopathological review. South African Med J. 2017;107(1):83–8.

11. Friedman RJ, Rigel DS, Kopf AW. Early Detection of Malignant Melanoma: The Role of Physician Examination and of the Skin. Cancer J Clin. 1985;35(3):130–51.

12. Gomez H, Hughes TJR, Nogueira X, Calo VM. Isogeometric analysis of the isothermal Navier–Stokes–Korteweg equations. Vol. 199, Computer Methods in Applied Mechanics and Engineering. 2010. p. 1828–40.

13. National Cancer Institute. Risk Factors: Age [Internet]. Available from: https://www.cancer.gov/about-cancer/causes-prevention/risk/age

14. Stewart BW, Wild CP. World cancer report 2014. World Health Organization. 2014.

15. Bray F, Ferlay J, Soerjomataram I. Global Cancer Statistics 2018 : GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. A Cancer J Clin. 2018;68:394–424.

16. Statics South Africa. Census in brief [Internet]. 2011. Available from: http://www.statssa.gov.za/census/census_2011/census_products/Census_2011_Census_in_brief.pdf

17. South African National Cancer Registry. Cancer in South Africa. Johannesburg. [Internet]. Available from: http://www.nicd.ac.za/index.php/centres/national-cancer-registry/

18. Gordon LG, Elliott TM, Wright CY, Deghaye N, Visser W. Modelling the healthcare costs of skin cancer in South Africa. BMC Health Serv Res. 2016;16(1):1–9.

19. Norval M, Kellett P, Wright CY. The incidence and body site of skin cancers in the population groups of South Africa. Photodermatol Photoimmunol Photomed. 2014;30(5):262–5.

20. National Health Laboratory Service. NCR Methodology [Internet]. 2006. Available from: www.nioh.ac.za/assets/files/NCR_methodology.pdf

21. Diallo M, Diadie S, Diatta BA, Ndiaye M, Diop A, Dieng MT. Skin cancers of the face in an African Black population. Arch Otolaryngol Rhinol. 2017;3(3):095–7.

22. Wu S, Han J, Laden F, Qureshi AA. Long-term ultraviolet flux, other potential risk factors, and skin cancer risk: A cohort Study. Cancer Epidemiol Biomarkers Prev. 2014;23(6):1080–9.

23. English DR, Armstrong BK, Kricker A, Winter MG, Heenan PJ, Randell PL. Case-control study of sun exposure and squamous cell carcinoma of the skin. Int J Cancer. 1998;77(3):347–53.

24. Fajuyigbe D, Young AR. The impact of skin colour on human photobiological responses. Pigment Cell Melanoma Res. 2016;29:607–18.

25. Chen J, Hu P, Zhou T, Zheng T, Zhou L, Jiang C, et al. Epidemiology and clinical characteristics of acute respiratory tract infections among hospitalized infants and young children in Chengdu, West China, 2009–2014. BMC Pediatr. 2018;18(216):1–8.

26. Stein L, Urban MI, O'Connell D, Xue QY, Beral V, Newton R, et al. The spectrum of human immunodeficiency virus-associated cancers in a South African black population: Results from a case-control study, 1995-2004. Int J Cancer. 2008;122:2260–5565.

27. Clemmesen J. Cancer epidemiology: shortcomings and possibilities. Environ Health Perspect. 1983;50:329–38.

28. Holick MF. Sunlight, UV-radiation, vitamin D and skin cancer: how much sunlight do we need? Reichrath J, editor. Advances in Experimental Medicine and Biology; 2008. 1-15 p.

29. Sivasakthivel T, Reddy K. Ozone layer depletion and its effects: A review. Int J Environ Sci Dev. 2011;2(1):30–7.

30. Gallagher RP, Lee TK, Bajdik CD, Borugian M. Ultraviolet radiation. Chronic Dis Can. 2010;29(1):51–68.

31. Dorak MT, Karpuzoglu E. Gender Differences in Cancer Susceptibility: An Inadequately Addressed Issue. Front Genet. 2012;3(268):1–11.

32. Brooke HL, Talbäck M, Martling A, Feychting M, Ljung R. Socioeconomic position and incidence of colorectal cancer in the Swedish population. Cancer Epidemiol. 2016;40:188–95.

33. Shin D, Lee E, Kim J, Guerra L, Naik D, Prida X. Association between the use of thiazide diuretics and the risk of skin cancers: A meta-analysis of observational studies. J Clin Med Res. 2019;11(4):247–55.

34. Saladi RN, Persaud AN. The causes of skin cancer: A comprehensive review. Drugs of Today. 2005;41(1):37.

35. Buchanan LN, Berktold J, Holman DM, Stein K, Prempeh A, Yerkes A. Skin cancer knowledge, awareness, beliefs and preventive behaviors among black and hispanic men and women. Prev Med reports. 2018;12:203–9.

36. Feiko R, Bruijnzeel PL, van Weelden H, Kiekens RC. Responses of black and white skin to solar-simulating radiation: Differences in DNA photodamage, infiltrating neutrophils, proteolytic enzymes induced, keratinocyte activation, and IL-10 expression. J Invest Dermatol. 2004;122(6):1448–55.

37. Ginde AA, Liu MC, Camargo Jr CA. Demographic Differences and Trends of Vitamin D Insufficiency in the US Population, 1988-2004. Arch Intern Med. 2009;169(6):626–32.

38. Boyle P, Levin B. World cancer report 2008 [Internet]. IARC Press; 2008. Available from: https://www.who.int/cancer/publications/world_cancer_report2008/en/

39. Boniol M, Autier P, Boyle P, Gandini S. Cutaneous melanoma attributable to sunbed use: Systematic review and meta-analysis. BMJ. 2012;345(7877):1–12.

40. LoConte NK, Gershenwald JE, Thomson CA, Crane TE, Harmon GE, Rechis R. Lifestyle Modifications and Policy Implications for Primary and Secondary Cancer Prevention: Diet, Exercise, Sun Safety, and Alcohol Reduction. Am Soc Clin Oncol. 2018;(38):88–100.

41. A Måsbäck NJ and HOJWCI. Risk of cutaneous malignant melanoma in relation to use of sunbeds: further evidence for UV-A carcinogenicity. Br J Cancer. 2000;82(9):1593–9.

42. Norval M, Wright CY. The Epidemiology of Cutaneous Melanoma in the White and Black African Population Groups in South Africa. Cutan Melanoma Etiol Ther. 2017;23–38.

43. Kiprono S, Chaula B, Beltraminelli H. Histological review of skin cancers in African Albinos: A 10-year retrospective review. BMC Cancer [Internet]. 2014;14(157):1–4. Available from: BMC Cancer

44. Karlehagen S, Andersen A, Ohlson CG. Cancer incidence among creosote-exposed workers. Scand J Work Environ Heal. 1992;18(1):26–9.

45. Singh M, Suman S, Shukla Y. New enlightenment of skin cancer chemoprevention through phytochemicals: In vitro and in vivo studies and the underlying mechanisms. Biomed Res Int. 2014;2014:1–18.

46. Omland SH, Ahlström MG, Gerstoft J, Pedersen G, Mohey R, Pedersen C, et al. Risk of skin cancer in HIV-infected patients: a Danish nationwide cohort study. J Am Acad Dermatol. 2018;18:30475–4.

47. City of Johannesburg [Internet]. [cited 2019 Apr 30]. Available from: https://www.joburg.org.za/about_/regions/Pages/Region E - Sandton, Alexandra/region-e.aspx

48. Sengayi M, Babb C, Egger M, Urban MI. HIV testing and burden of HIV infection in black cancer patients in Johannesburg, South Africa: a cross-sectional study. BMC Cancer. 2015;15(144):1–12.

49. International Classification of Diseases for Oncology [Internet]. [cited 2018 Apr 24]. Available from: http://codes.iarc.fr/

50. Pfister H. Chapter 8: Human Papillomavirus and Skin Cancer. In: Journal of the National Cancer Institute Monographs. Oxford University Press; 2003. p. 52–6.

51. Eisemann N, Waldmann A, Geller AC, Weinstock MA, Volkmer B, Greinert R, et al. Non-Melanoma Skin Cancer Incidence and Impact of Skin Cancer Screening on Incidence. Soc Investig Dermatology. 2014;134(1):43–50.

52. Solar ultraviolet radiation exposure and human health in South Africa: Finding a balance. South African Med J. 2012;102(8):665–6.

53. Stein L, Urban MI, Weber M, Ruff P, Hale M, Donde B, et al. Effects of tobacco smoking

on cancer and cardiovascular disease in urban black South Africans. Br J Cancer. 2008;98(9):1586–92.

54. Gudrun K, Griet J, Maarten S, Jef D, Ann C, Boris L, et al. Development and evaluation of a wood smoke biomarker. Vis Technol. 2017;1–131.

55. Bundesinstitut für Risikobewertung. Highly refined mineral oils in cosmetics: Health risks are not to be expected according to current knowledge. 2015;014:1–27.

56. Wood HB. Paraffin not productive of cancer. Cancer Res. 1929;13(1):97–102.

APPENDICES

Appendix I: Ethical clearance certificate for the research

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Ms BC Ndlovu, et al
School of Public Health
Division of Epidemiology and Biostatistics
Medical School
University

E-mail: BabongileN@nicd.ac.

CC: Supervisor: Drs E Singh and L Kuonza <ElviraS@nicd.ac.za>
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 20/12/2018

REF: *R14/49*

PROTOCOL NO: **M181191** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *Skin cancer risk factors in black South Africans of the Gauteng Province in the Johannesburg Cancer Study, 1995-2016*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Ms BC Ndlovu, et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M181191

NAME: (Principal Investigator)	Ms BC Ndlovu, et al
DEPARTMENT:	School of Public Health Division of Epidemiology and Biostatistics Medical School University
PROJECT TITLE:	Skin cancer risk factors in black South Africans of the Gauteng Province in the Johannesburg Cancer Study, 1995-2016
DATE CONSIDERED:	30/11/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Drs E Singh and L Kuonza
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	20/12/2018

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 Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/We fully understand the conditions under which I am/we are authorised 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 to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date of the meeting when the study was initially reviewed. In this case, the study was initially reviewed in **November** and will therefore reports and re-certification will be due early in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

07 JANUARY 2019
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix II: Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG | FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I BABONGILE CONFIDENCE NDLOVU (Student number: 1033257) am a student registered for the degree of MSc Epidemiology (Field Epidemiology) in the academic year 2019.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

Signature: _____ Date: 12 December 2019

Appendix III: Dataset Gate-keeper Permission letter

NATIONAL HEALTH LABORATORY SERVICE
National Cancer Registry

National Cancer Registry
1 Modderfontein Road, Sandringham, Johannesburg 2131
Tel: +27 (0)11 555 0548 Fax: +27 (0)11 386 6516

Date: 29 October 2018

Faculty Health Sciences
University of the Witwatersrand
The Human Research Ethics Committee

Dear Chairperson

RE: Authorization to use Johannesburg Cancer Study data from the South Africa National Cancer Registry

Ms Babongile C Ndlovu (student number: 1033257) is an MSc Epidemiology (Field Epidemiology) student at the University of the Witwatersrand and a Field Epidemiology Training Program (FETP) Resident, part of the National Institute of Communicable Diseases (NICD) who is currently placed at the National Cancer Registry (NCR).

This letter authorizes the aforementioned student the usage of a dataset from the Johannesburg Cancer Study (JCS) based at the South African National Cancer Registry (SA-NCR) for the research topic "**Risk factors in Johannesburg Cancer Study for skin cancers in a black population in the Gauteng Province, South Africa 1995-2016".** The JCS recruited adult (18+ years old), consenting black South African patients in Johannesburg healthcare facilities presenting with a confirmed diagnosis of cancer. The JCS data is stored in STATA database under the custodianship and curatorship of the SA-NCR. Records that have skin cancer as a diagnosis will be used for risk factor analysis in the current study. Controls will be randomly selected from all other JCS participants whose cancers are not skin cancer. The de-identified dataset will be provided to Babongile C Ndlovu upon receipt of ethical clearance from the University of the Witwatersrand's Human Research Ethics Committee.

The nature of the research project does not require the use of patient identifiers as participants were assigned unique identifiers from recruitment. The NCR has an ethics clearance from the University of Witwatersrand's Human Research Ethics Committee to conduct sub-studies from the JCS (Clearance Certificate no. M1606103, dated 09/12/2016). Additionally, Ms Babongile C Ndlovu is employed by the SA-NCR and is involved in data processing. She has signed confidentiality agreements with the National Cancer Registry.

Ms Ndlovu is hereby granted permission to use data the JCS data for fulfillment of her MSc degree in Epidemiology.

Regards,

Dr Elvira Singh
Head: National Cancer Registry
National Health Laboratory Service
Tel: +27(0)11 386 6407 | Mobile: +27(0)84 587 7010
elvira.singh@nioh.nhls.ac.za | www.ncr.ac.za | www.nhls.ac.za

Appendix IV: Ethical clearance certificate for primary study

R14/49 Dr Elvira Singh et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M1606103

NAME: (Principal Investigator)	Dr Elvira Singh et al
DEPARTMENT:	Medical Research Council National Health Laboratory Services University of the Witwatersrand
PROJECT TITLE:	Johannesburg Cancer Study
DATE CONSIDERED:	Adhoc
DECISION:	Approved unconditionally
CONDITIONS:	Previously Dr Lara Stein, Cancer Case-Control Study (Previously M981119, M040445 and M090361)
SUPERVISOR:	
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	09/12/2016

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 Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in March and will therefore be due in the month of March each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix V: JCS informed consent

JOHANNESBURG HOSPITALS NHLS/ CERG CANCER EPIDEMIOLOGY STUDY

Interviewer check list

Note to the Interviewer: **Study no:_____**

This is a checklist for you and a Consent Form for the patient.
Please ask the questions in your own words.
Tick ☑ the boxes and fill in the blanks ***as you complete that task.***

My name is _____(*name of interviewer)*

I work at the National Health Laboratory Service and would like to ask you some questions.
Please ask:

1. *Has the patient ever been diagnosed with a* ***cancer prior to this cancer****?* *yes* ☐ *no* ☐ *not known* ☐
If yes, thank the patient for their time but DO NOT proceed with the interview.

2. *When was the patient* ***diagnosed with the PRESENT CANCER?*** ☐ *more than 6 months ago*

☐ *less than 6 months ago*

☐ *has not yet received diagnosis.*

If the patient was diagnosed ***more than 6 months ago****, thank the patient but DO NOT INTERVIEW THE PATIENT.*
If the patient was diagnosed less than 6 months ago, make sure that:

- *the patient has* ***NOT had any chemotherapy or radiotherapy****;*
- *the patient has* ***NOT been interviewed for this study before***

……*Tick the box once you have done this.* ☐

PATIENT CONSENT FORM

A: We would like you to take part in a study to find out if your exposure to substances in the environment, your circumstances and habits, your occupation, previous illnesses, and/or inherited factors play a role in the illness you have developed.

We have chosen a group of patients from this ward / clinic because of their current illness so that we can make comparisons between illnesses. We are asking you to spend 20 – 30 minutes answering questions about yourself, your family, and your work. *Do you have any questions so far?*

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

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

Signature_____ Date _____

B: We would also like to take 3 – 4 teaspoons of blood from you for future research into the causes of your illness. No names will be attached to the sample tubes.

The blood we take for this study will not be tested immediately; it will be frozen. There is no time limit to how long it will be stored. It may be tested for evidence of various infections including HIV; it may be tested for substances (cells, proteins, other body chemicals) which might make it easier for you to have become ill. It may also be tested for inherited factors which might make it more likely for you to have developed the illness you now have. These tests will help us to understand your and other patients' illness better and, perhaps, prevent others from getting it. We only need to take blood from you once. At the current time we cannot provide details of what will be looked at, as this is not yet known, but we give assurance that no research will be done without the approval of the Wits Human Research Ethics Committee as well as the applicable Research Ethics Committees at the analysis sites.

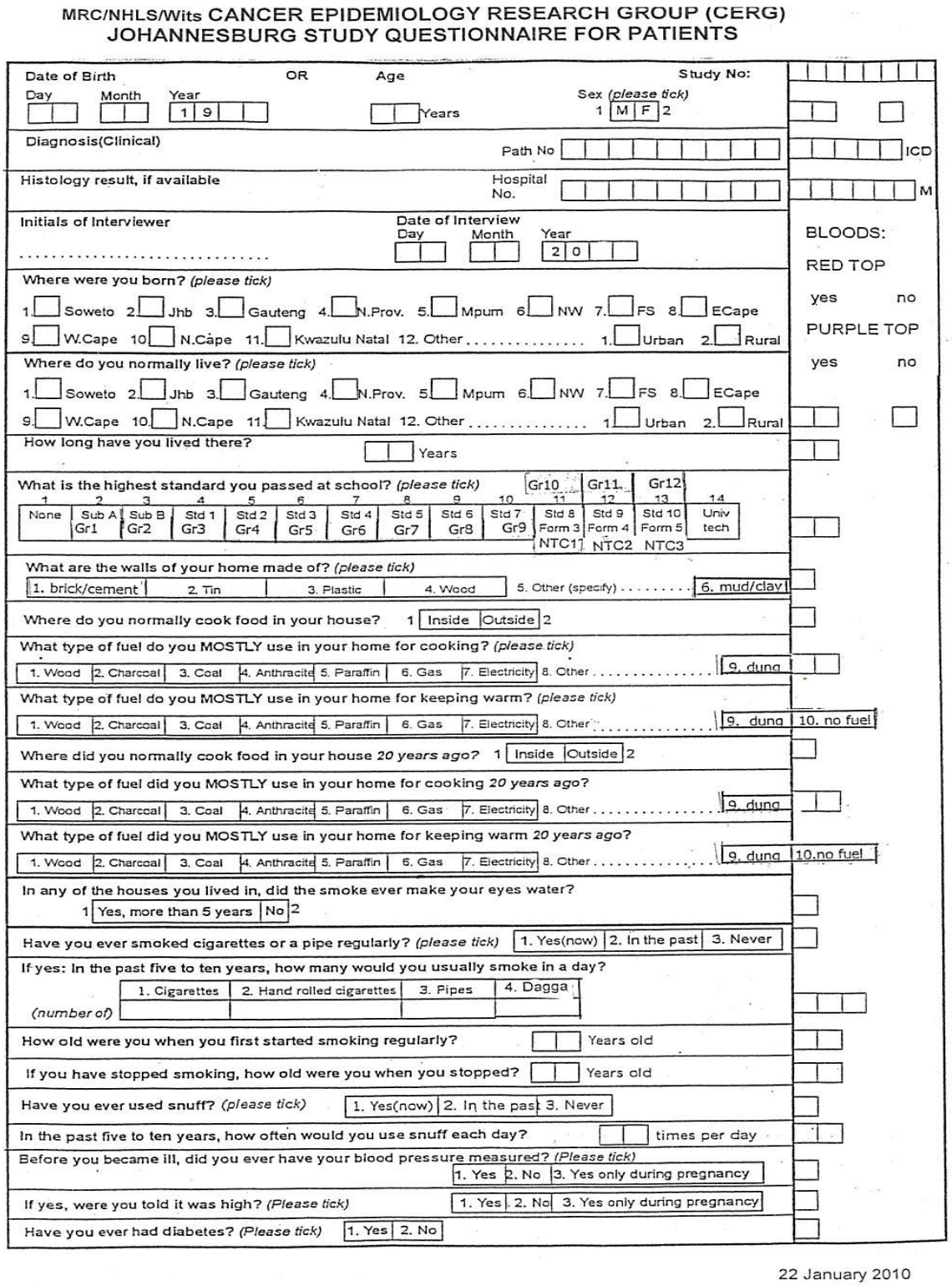
This is a consent form. It says in writing what I have just told you. Please sign and date it here to show that you have understood what I have told you and that you willingly agree to have your blood collected.

Signature_____ Date _____

Signature of witness _____Date _____
(in case verbal consent given)

For enquiries telephone: Tonicah Maphanga 011 489 9150
tonicah.maphanga@nhls.ac.za *February 2015*

Appendix VI: JCS questionnaire



MRC/NHLS/Wits CANCER EPIDEMIOLOGY RESEARCH GROUP (CERG)
JOHANNESBURG STUDY QUESTIONNAIRE FOR PATIENTS

Date of Birth OR Age Study No:
Day Month Year 1 9 Years Sex (please tick) 1 M F 2

Diagnosis(Clinical) Path No ICD

Histology result, if available Hospital No. M

Initials of Interviewer ..... Date of Interview Day Month Year 2 0

BLOODS:
RED TOP yes no
PURPLE TOP yes no

Where were you born? (please tick)
1. Soweto 2. Jhb 3. Gauteng 4. N.Prov. 5. Mpum 6. NW 7. FS 8. ECape
9. W.Cape 10. N.Cape 11. Kwazulu Natal 12. Other ..... 1. Urban 2. Rural

Where do you normally live? (please tick)
1. Soweto 2. Jhb 3. Gauteng 4. N.Prov. 5. Mpum 6. NW 7. FS 8. ECape
9. W.Cape 10. N.Cape 11. Kwazulu Natal 12. Other ..... 1. Urban 2. Rural

How long have you lived there? Years

What is the highest standard you passed at school? (please tick) Gr10 Gr11 Gr12

1	2	3	4	5	6	7	8	9	10	11	12	13	14
None	Sub A Gr1	Sub B Gr2	Std 1 Gr3	Std 2 Gr4	Std 3 Gr5	Std 4 Gr6	Std 5 Gr7	Std 6 Gr8	Std 7 Gr9	Std 8 Form 3 NTC1	Std 9 Form 4 NTC2	Std 10 Form 5 NTC3	Univ tech

What are the walls of your home made of? (please tick)
1. brick/cement 2. Tin 3. Plastic 4. Wood 5. Other (specify) ..... 6. mud/clay

Where do you normally cook food in your house? 1 Inside Outside 2

What type of fuel do you MOSTLY use in your home for cooking? (please tick)
1. Wood 2. Charcoal 3. Coal 4. Anthracite 5. Paraffin 6. Gas 7. Electricity 8. Other ..... 9. dung

What type of fuel do you MOSTLY use in your home for keeping warm? (please tick)
1. Wood 2. Charcoal 3. Coal 4. Anthracite 5. Paraffin 6. Gas 7. Electricity 8. Other ..... 9. dung 10. no fuel

Where did you normally cook food in your house *20 years ago?* 1 Inside Outside 2

What type of fuel did you MOSTLY use in your home for cooking *20 years ago*?
1. Wood 2. Charcoal 3. Coal 4. Anthracite 5. Paraffin 6. Gas 7. Electricity 8. Other ..... 9. dung

What type of fuel did you MOSTLY use in your home for keeping warm *20 years ago*?
1. Wood 2. Charcoal 3. Coal 4. Anthracite 5. Paraffin 6. Gas 7. Electricity 8. Other ..... 9. dung 10.no fuel

In any of the houses you lived in, did the smoke ever make your eyes water?
1 Yes, more than 5 years No 2

Have you ever smoked cigarettes or a pipe regularly? (please tick) 1. Yes(now) 2. In the past 3. Never

If yes: In the past five to ten years, how many would you usually smoke in a day?

	1. Cigarettes	2. Hand rolled cigarettes	3. Pipes	4. Dagga
(number of)				

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

If you have stopped smoking, how old were you when you stopped? Years old

Have you ever used snuff? (please tick) 1. Yes(now) 2. In the past 3. Never

In the past five to ten years, how often would you use snuff each day? times per day

Before you became ill, did you ever have your blood pressure measured? (Please tick)
1. Yes 2. No 3. Yes only during pregnancy

If yes, were you told it was high? (Please tick) 1. Yes 2. No 3. Yes only during pregnancy

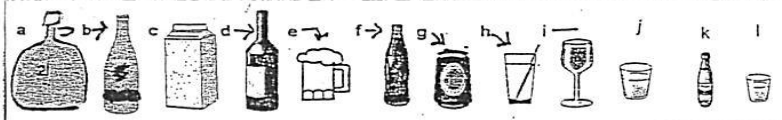
Have you ever had diabetes? (Please tick) 1. Yes 2. No

22 January 2010

Before you became ill, about how much wine, beer or spirits did you drink on average each week?
(Please indicate glass/bottle size when you select block for each type of drink - eg. 3 large glasses of maize beer per week would be 3 e if none then 0

BEER			SPIRITS		WINE	CIDER; other	OTHER
sorghum (cartoon)	homemade (specify type)	commercial	Homemade	commercial		commerical alcoholic fruit drinks	SPECIFY

a: 2l (wine bottle)
b: bottle (1 litre)
c: 1l carton
d: 750ml (wine bottle)
e: 500ml (beer glass)
f: 375ml (half jack/pint)
g: 340ml (beer can/dumpy)
h: 250ml glass
i 200ml (wine) glass/nip
j : 100ml (small glass)
k 50ml (miniature airplane bottle)
l 25ml (tot)
mother (please specify)



Are you? *(please tick)*
1. ☐ Single (never been married) 2. ☐ Married(living as married) 3. ☐ Widowed 4. ☐ Separated

How many husbands/wives have you had?

FOR WOMEN ONLY: Have you ever been pregnant? *(please tick)* 1 Yes No 2
If yes, how many times have you been pregnant? ☐☐
If yes, how many times have you had a miscarriage? ☐☐
If yes, how many of your children were born alive? ☐☐

FOR MEN ONLY: How many children *(dead or alive)* do you have?

ALL: How many mothers / fathers do the children have?

ALL: How old is your oldest child now? *(include dead & alive)* ☐☐ Years old

ALL: How old is your youngest child now? *(include dead & alive)* ☐☐ Years old

ALL: How many boyfriends/girlfriends have you had?

FOR WOMEN ONLY
How old were you when your periods began? ☐☐ Years old

Age now (from previous page) _____

Age at first birth _____

Age at last birth _____

Have your periods ended? Yes ☐1 No ☐2 Not sure ☐3 If yes, how old were you when they ended? ☐☐ years old

If Yes, did your periods stop: ☑

1. naturally	2. due to surgery	3. due to medical treatment	4. due to IC use	5. other	6. unknown

	Oral	Injectable
Have you ever taken contraceptives?	1 Yes No 2	1 Yes No 2
If yes, how old were you when you started taking them?	☐☐	☐☐ Years old
How old were you when you stopped taking them?	☐☐	☐☐ Years old
If yes, for how long in total did you take them?	☐☐	☐☐ Years
Interruptions? ☑	1 Yes No 2	1 Yes No 2

Main reason for stopping, the last time you stopped using the method: ☐☐ ☐☐

1 Nausea 2 high BP 3 headaches 4 wt.Gain 5.changed menstrual pattern 6. menopause 7.sterilization 8.hysterectomy 9. no partner 10. to become pregnant 11 other 0.no specific reason

Have you ever had a 'pap' smear?☑

0. Never	1. Yes	2. current illness only	9. Can't remember		If yes, how many?	Age at first pap(yrs)	Age at last pap (yrs)

FOR ALL: Describe your usual or past **occupation** (eg. Driver, machine operator).....

Describe what your usual **workplace** does or did (eg. A bank, a chemical factory, a gold mine.....

What language do you speak most at home? ☐
What language does/did your father speak? ☐
What language does/did your mother speak? ☐

1. Zulu 2. Xhosa 3. Sotho 4.Pedi 5. Tswana 6. Venda 7. Swazi 8. Shangaan 9. Ndebele
10 English 11. Afrikaans 12. Other

22 January 2010

Study number: _____

Cancer Epidemiology Research Group **Case-Control Study**

Antiretroviral Drug Usage

*Please ask **ALL PATIENTS** the following questions AFTER you have completed the standard questionnaire. Make sure that you emphasize that the information is voluntary and confidential.*

Have you ever been tested for HIV (before current test)? **Yes** **No** (circle one)

If YES, proceed: Were you tested**: before this illness / at time of current illness only** (circle one)

Were you given the test results? **Yes** **No** (circle one)

If YES, proceed: Are you willing to disclose your status? **Yes** **No** (circle one)

If YES, proceed: Are you HIV: **positive** **negative** (circle one)

Date of last/current test (mm/yyyy): __________

If POSITIVE, proceed:
Have you ever taken anti-Retroviral medicines for your HIV infection? **Yes** **No** (circle one)

(Be careful to explain to the patient that we mean "Western" medicine/pills/capsules specifically for the HIV itself, NOT for opportunistic infections.)

If YES, Proceed:

From: _____ (start date) To: _____ (end date)

From: _____ (start date) To: _____ (end date)

From: _____ (start date) To: _____ (end date)

The ARV drugs were provided by (tick all that apply):

- ☐ Private practitioner
- ☐ Public hospital/clinic
- ☐ NGO
- ☐ Study/ clinical trial

Thank the patient for answering these extra questions even if they only answered the first one.

5 JANUARY 2007 CERG Margaret Urban 489 9713