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Mesothelioma incidence and mortality in South Africa from 2003 to 2013

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MESOTHELIOMA INCIDENCE AND MORTALITY IN SOUTH AFRICA FROM 2003 TO 2013

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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 and Biostatistics

Johannesburg, February 2018

DECLARATION

I, Dr Kasongo Michel Muteba, am submitting my research report in partial fulfillment of the requirements of the MSc in the field of Epidemiology and Biostatistics, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand. This report has not been submitted previously for any degree or examination at this or any other university. I hereby declare that this research report is my own work. Where I have used the thoughts or ideas of others, the required referencing conventions have been adhered to.

Signed: 

Date: 27 February 2018

DEDICATION

I dedicate this research report to my wife, Jenny, and my children, Mikaela, Elim, Isaac and Jordan Muteba.

CONFERENCE PRESENTATION FROM THIS STUDY

1. Muteba KM, Sartorius B, Nelson G. Trends in mesothelioma incidence and mortality in South Africa using four different data repositories (2003-2013). Annual SASOM workshop, 16 August 2017, Kuruman, Northern Cape, South Africa.
2. Muteba KM, Sartorius B, Nelson G. Trends in mesothelioma incidence and mortality in South Africa using four different data repositories (2003-2013). School of Public Health Biannual Research Day, 27 November 2017, University of the Witwatersrand, Johannesburg, South Africa.

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ABSTRACT

Background

The incidence of mesothelioma in South Africa was expected to increase until around 2022 because of the high production of asbestos in the 1990s and a latency period of 20 to 40 years. Not enough research has been done to determine the burden of mesothelioma and evaluate the impact of asbestos ban policies in South Africa since 2001. This study investigated the burden of mesothelioma among South African men and women from 2003 to 2013, and compared the trends in mesothelioma by province, using four different data repositories.

Methods

A review of records from Statistics South Africa (Stats SA), the National Cancer Registry (NCR), the Pathology Automation database of the National Institute for Occupational Health, and the Asbestos and Kgalagadi Relief Trusts (ART/KRT), were used to estimate the annual mesothelioma incidence and mortality by province of South Africa from 2003 to 2013. Age-standardized incidence and mortality rates using direct standardization, and the average annual percentage change were calculated using the mid-year populations of South Africa as reported by Stats SA for each province, using the World Health Organization World standard population. A negative binomial regression analysis was conducted to identify factors associated with mesothelioma deaths.

Results

The NCR reported 1 242 new cases of mesothelioma from 2003 to 2010. The average incidence rate per annum was 155 cases, with an age-standardized incidence rate of 0.619 cases per 100 000 world population in 2003, which gradually decreased to 0.399 by 2010. The official statistics from Stats SA reported an average of 194 mesothelioma deaths per annum between 2003 and 2013, or 2132 mesothelioma deaths in total. During the same period, 385 and 499 cases were recorded in the PATHAUT and the ART/KRT databases, respectively.

The average age at diagnosis was 63 years in the NCR data, while the average age at death varied from 63 to 65 years in the StatSA and PATHAUT data, with a sex ratio of 5:1 in the PATHAUT data, and 3:1 in the other databases.

The Northern Cape had the highest number of mesothelioma deaths across the years of study, with the age standardized mortality rates varying from 3 to 7 cases per 100 000 standard population. The average annual percent change was -1.65%, showing a decreasing trend over time. The annual age standardized mortality rates were higher than the age standardized incidence rates, decreasing from 0.63 to 0.57 mesothelioma deaths per 100 000 World standard population from 2003 to 2013.

There was overwhelming evidence of associations of age, sex, race, and province of death with mesothelioma deaths ($P<0.001$). The adjusted mortality rate ratio was 1.3 times higher in males compared to females, 5 times higher in the Northern Cape compared to the Western Cape, 21 times higher in those older than 75 years compared to those younger than 40 years, and 3 times higher in Whites compared to Blacks.

Conclusion

The patterns of mesothelioma observed in this study suggest a decreasing trend in mesothelioma incidence and mortality in South Africa, contrary to previous predictions anticipating an increasing trend until 2022. It can therefore be assumed that the peak of mesothelioma has occurred earlier than expected. Record linkage of the different data repositories could be used to confirm under-reporting of the mesothelioma official statistics.

Key words: *age-standardized mortality rates, asbestos related diseases, negative binomial regression, average annual percent change*

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ABBREVIATIONS

AAPC	Average Annual Percent Change
ART	Asbestos Relief Trust
ARTMis	Asbestos Relief Trust Management Information System
ASIR	Age-standardized incidence rates
ASMR	Age-standardized mortality rates
CDR	Crude Mortality Rate
CI	Confidence Interval
IARC	International Agency for Research on Cancer
IQR	Interquartile range
KRT	Kgalagadi Relief Trust
NCR	National Cancer Registry
NIOH	National Institute for Occupational Health
PATHAUT	Pathology Automation System
SD	Standard deviation
Stats SA	Statistics South Africa
WHO	World Health Organization

DEFINITIONS OF TERMS

- Mesothelioma death: death caused by the development of mesothelioma that has been confirmed by a histopathological test and recorded on the death certificate as the primary or secondary cause of death
- Average Annual Percent Change: A measure that characterizes the trend in cancer over time
- World standard population: reference population used by the WHO since 2001 to calculate age-standardized estimate rates.

CHAPTER 1 : INTRODUCTION

This chapter describes the global and South African burdens of mesothelioma and highlights the public health importance of the study. The relevant literature on mesothelioma is also reviewed in this section before stating the aim and specific objectives of the study.

1.1 Background

Malignant mesothelioma is a rare cancer that affects the pleura, the peritoneum, the pericardium and the testes tunica. It has a long latency period, varying from 20 to 70 years (1); affected individuals survive for only a short period after diagnosis, with a median survival ranging from 9 to 17 months (2). The insidious nature of mesothelioma and poor diagnostic facilities make diagnosis difficult in developing countries, and a considerable number of cases are often diagnosed during a post-mortem examination. Almost all people who develop mesothelioma have a history of occupational or environmental exposure to asbestos fibres (3). Mesothelioma and asbestosis have been used as indicators of the burden of asbestos-related disease in a population (4).

Despite the ban on the use of asbestos in most countries since the 1990s, the global burden of mesothelioma is still rising and its mortality is expected to peak by the year 2020 because of the long latency that characterizes the disease (5). The World Health Organization stated that approximately 43 000 deaths occur annually due to mesothelioma and control measures to eliminate all asbestos-related diseases, globally, is ongoing (5,6).

South Africa produced and used asbestos for over a century and the highest production occurred during the 1970s (7,8). Regulations for the prohibition of the usage, manufacturing, import and export of asbestos and asbestos containing materials in South Africa were published in 2008 under section 24B of the Environment Conservation Act, by the Department of Environmental Affairs and Tourism (9).

Provinces that have mined asbestos are Limpopo, Mpumalanga and the Northern Cape in what are called the “Asbestos Mountains”, lying from Kuruman to Prieska, where the crocidolite or blue asbestos was mined (Fig 1.1) (10). The then Transvaal produced amosite

or brown asbestos. Chrysotile or white asbestos was produced in the Eastern Transvaal (Barbeton, Msauli) (7).

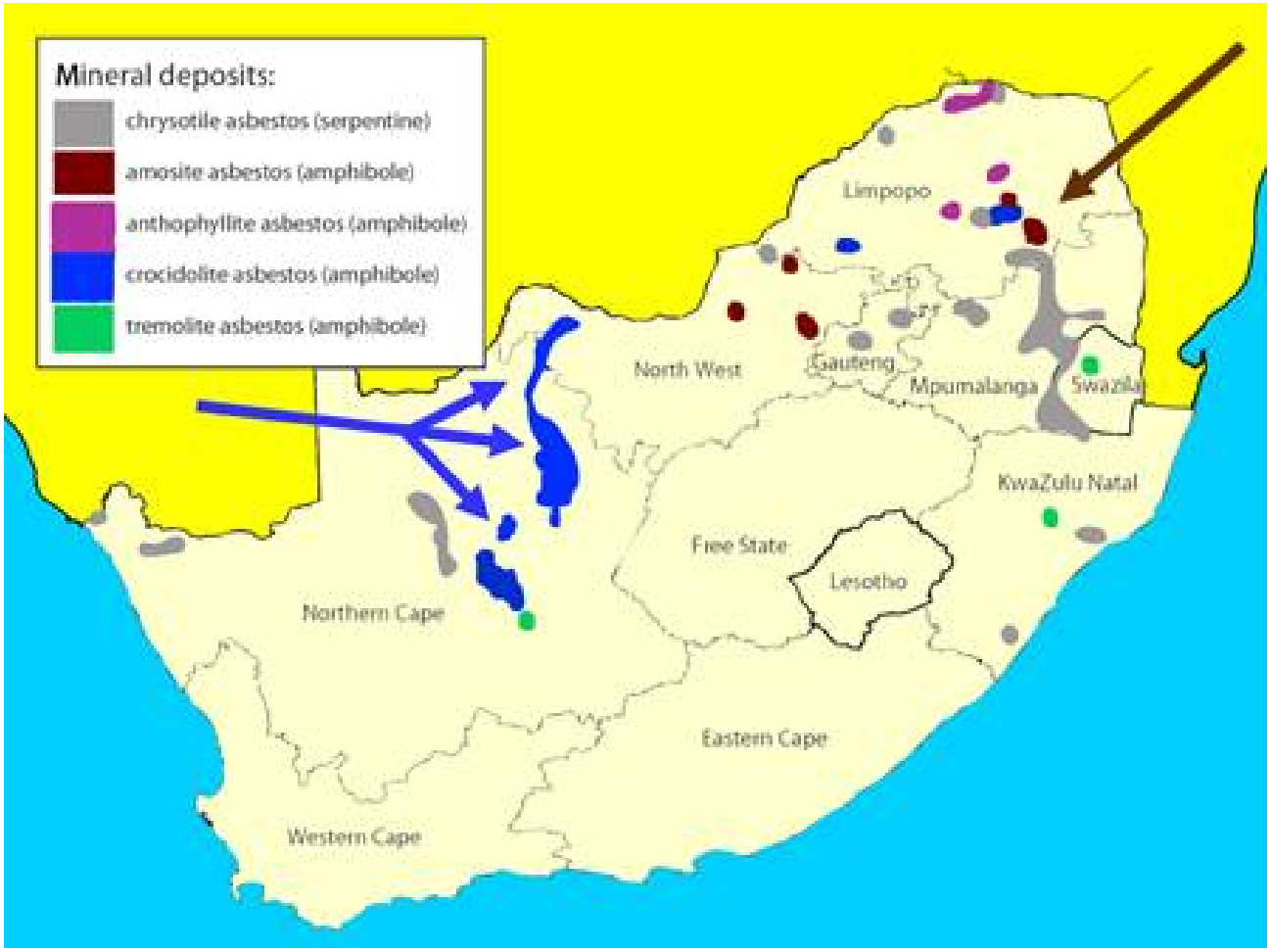


Figure 1.1 Map of South Africa showing geographical distribution of asbestos

There are uncertainties about the burden of mesothelioma in South Africa as different studies have provided different estimates for similar periods. For example, the WHO of 2011 estimated that South Africa had 2 322 deaths due to mesothelioma for the period 1994 – 2008 (5). Official statistics reported around 200 cases per year and an estimated 2 509 deaths due to mesothelioma from 1995 to 2007, using data obtained from Statistics South Africa (Stats SA) (11). Another study estimated the number of deaths attributed to mesothelioma in South Africa from 1995 to 2008 at 2 497 (12). The varying estimates of the disease reported by different studies may be due to the utilization of differing data sources and collation methods. Furthermore, issues related to poor reporting systems, the migrant labour system in South Africa, poor cancer case ascertainment, and other competing causes of death, such as HIV/AIDS (which, in the past, led to a reduced life expectancy) may have also contributed to estimation uncertainty and lower than expected mesothelioma mortality rates in South Africa.

The reported rates from local studies may well be underestimated since South Africa was one of the major producers of asbestos, and mesothelioma incidence rates (13) and mortality rates had previously been found to be lower than expected (5). The quality of cancer data in the country was also highlighted by Singh and colleagues (2015) who reported that there was poor reporting by private laboratories, especially from 2005 to 2007 (14). Based on the uncertainty about the validity of previous estimates, and conflicting figures reported in the literature, there was a need to more accurately estimate the current mesothelioma incidence and mortality figures of South Africa by harmonizing data from the available mesothelioma data repositories in the country.

This study therefore aimed to determine the trends in age standardized incidence and mortality rates of mesothelioma in South Africa from 2003 to 2013 by looking at records from four different data sources, to aid public health surveillance and monitoring of malignant mesothelioma cases.

1.2 Literature review

1.2.1 Epidemiology of malignant mesothelioma

The WHO report on mesothelioma mortality (2011) estimated that, from 1994 to 2008, a total of 92 253 deaths occurred due to mesothelioma in 83 countries, with an average age at death of 70 years, an age-adjusted mortality rate of 4.9 per million, and a sex ratio of 3.6 males to 1 female. According to the same report, an estimated 2 322 deaths due to mesothelioma for 12 reporting years were reported in South Africa, which accounted for 2.5% of the global mesothelioma mortality rate (5). In the United Kingdom, a study on mesothelioma has reported that, for the year 2010, five times more men than women were affected and that 97% of mesothelioma cases in males and 82.5% in females were attributable to occupational exposure (15). In 2010, the United Kingdom reportedly had the highest mesothelioma mortality rate in Europe with 0.6 female and 3.1 male deaths per 100 000 per year; the most affected age group was those aged 60 to 80 years (16).

The International Agency for Research on Cancer (IARC) estimated that approximately 43 000 mesothelioma deaths occurred in Europe and America in the year 2005. Local studies have found that, in relation to mesothelioma death occurrence in South Africa, the average

age at death was 63.4 years; the age-adjusted mortality rate was 6.7 per million, with a male to female ratio of 3.3:1(5). These reports also showed that deaths due to mesothelioma in South Africa occurred at a younger age compared to those in Europe and North America, although the sex ratios were not significantly different.

1.2.2 Asbestos and mesothelioma

It has been proven that prior exposure to asbestos fibres is a causal factor for mesothelioma (17). Exposure to asbestos fibres can occur in occupational or non-occupational circumstances. Occupational asbestos exposure has occurred in asbestos miners, shipyard workers, electrical installation or insulation workers, and demolition workers. Non-occupational asbestos (environmental) exposure has been reported in the neighbourhoods of asbestos mines and asbestos-product manufacturing facilities, or mines dumps that are contaminated with asbestos fibres. Other non-occupational (domestic) exposure has been documented in those handling the clothes of workers who were directly exposed to asbestos dust (18). Asbestos is a fibrous mineral of which there are six different types: chrysotile, crocidolite, amosite, anthophyllite, tremolite, and actinolite. Exposure to these fibres has the potential to lead to asbestos-related diseases (asbestosis, mesothelioma and asbestos-related lung cancer), with a mesothelioma relative risk increasing by between 1% and 4% per fibre-year/ml (19). People exposed to asbestos will show signs of disease only 20-50 years after their first exposure (20). Symptoms include cough, shortness of breath, chest pain, fatigue hoarseness, nausea and vomiting, weight loss, constipation and abdominal pain (21).

Some studies have been conducted in the USA about the possible role of infection with simian virus 40 (SV40) in increasing the risk of mesothelioma occurrence (22). It should be noted that crocidolite and the other “straight fibre” amphibole types are mainly associated with mesothelioma development, unlike chrysotile (serpentine) which is primarily associated with lung cancer (17,23).

1.2.3 Mesothelioma diagnosis and survival

Trends in the incidence of mesothelioma in developed countries have been well reported due to available diagnostic methods such as MESOMARK and SOMAmer panel blood tests, MRIs, CT scans and PET scans, which can detect mesothelioma at stage I (5) when the cancer is still localized (24,25). These diagnostic methods are not readily available in most

developing countries where mesothelioma is frequently diagnosed at stage IV (late stage) or post-mortem due to the rapid progression of the cancer (26,27). The issues of mesothelioma diagnosis are similar to those regarding the diagnosis of asbestosis. Clinicians have relied on Chest X-ray radiographs to identify diseases related to asbestos exposure and therefore many of the potential cases with poor quality X-ray radiographs have been missed (28).

The prognosis of malignant mesothelioma is known to be very poor. Results from a 2012 study in Ireland showed that 71% of patients died within one year of diagnosis and less than 15% survived beyond two years (29). It should be noted that, because of the high fatality rate and the short survival period, as for pancreatic cancer, the incidence rate of mesothelioma approximates its mortality rate (30).

1.2.4 Mesothelioma incidence and mortality in South Africa

It is suspected that South Africa has a relatively high mesothelioma incidence (12) but only a few studies have been published. These have shown discrepancies in estimates, highlighting the uncertainty regarding the accuracy of the calculated estimates. For example, a study reported an estimated 2 497 deaths attributed to mesothelioma from 1995 to 2008 (12). Conversely, a report by the WHO calculated approximately 2 322 deaths due to mesothelioma from 1994 to 2008 (5). The period in which Nattey and Kielkowski (12) conducted their study was included in the period of the WHO study (5). However, the WHO study reported 175 fewer deaths attributed to mesothelioma than the study by Nattey and Kielkowski.

In 1984, South Africa accounted for the highest rate of mesothelioma in the world, with standardized incidence rates for men ranging from 2.48 to 3.29 per 100 000 person-years (13). However, only 2 509 deaths were identified from 1995 to 2007 in South Africa. This figure was very low when compared to Australia which produced crocidolite asbestos on a much smaller scale than South Africa, but reported more deaths attributed to mesothelioma (11). Nonetheless, both Zwi et al. and Kielkowski et al. agree that mesothelioma cases are underreported in South Africa (8).

1.3 Problem statement

The mining, import and use of asbestos in South Africa was banned in 2008. It was expected that this would impact on the mesothelioma incidence and mortality in the country. However, the paucity of literature on the burden of mesothelioma in South Africa hinders the ascertainment of the impact of the ban; and poor monitoring systems remain a challenge. Furthermore, the legacy of industrial activities involving the use of asbestos in South Africa cannot be ignored (31); asbestos dust has polluted the air in communities around abandoned mines, asbestos fibre mine tailings dumps and asbestos cement products, continuing to put current and future populations at risk of developing mesothelioma and other asbestos related diseases (32). There was a need for a reliable study on the burden of mesothelioma mortality in South Africa in the post-asbestos era.

1.4 Justification

There is no complete database that reports mesothelioma cases and deaths in South Africa. The poor diagnostic methods, the rarity of mesothelioma, and the short survival time after diagnosis are factors that have contributed to the under-reporting of mesothelioma incidence and deaths in South Africa in the last decade. It is therefore important to explore the possibility of comparing trends and, if possible, the linking of different repository databases for accurate quantification of the burden of mesothelioma in South Africa.

The results of this study provide more information and consistent data on mesothelioma in South Africa and will potentially contribute to better epidemiologic surveillance of malignant mesothelioma incidence and mortality.

1.5 Aim and Objectives

This study aimed to determine the burden of mesothelioma in South Africa from 2003 to 2013, using available data, by evaluating information from different data sources and calculating incidence and mortality rates of mesothelioma for each province of South Africa.

The objectives of the study were:

- To determine and compare, by province, the annual burden of mesothelioma in South Africa, from 2003 to 2013, using data from the Stats SA, NCR, PATHAUT, and ART/KRT;
- To describe the annual mesothelioma age-standardized incidence and mortality rates, using NCR and Stats SA data from 2003 to 2013;

- To determine factors associated with mesothelioma mortality in South Africa from 2003 to 2013, using data from Stats SA.

CHAPTER 2 : METHODS

A brief description of the South African population and the different data sources containing information about mesothelioma cases in South Africa, as well as a description of the processes used from data collation to data analysis, are outlined in this chapter. Relevant statistical data analyses techniques are also described.

In this temporal record review study, secondary data for identifying mesothelioma cases from 2003 to 2013 were collated from four administrative databases: Stats SA, the National Cancer Registry of South Africa (NCR), the PATHAUT database, and the Asbestos and Kgalagadi Relief Trusts (ART/KRT).

2.1 Study Population

The study population included all South African men and women who, from 2003 to 2013, were diagnosed with mesothelioma and recorded in the Stats SA, NCR, ART/KRT or PATHAUT databases, and people who died from mesothelioma as recorded by Stats SA or captured on the PATHAUT database. All non-South Africans were excluded.

2.2 Data Sources

2.2.1 Statistics South Africa (Stats SA)

Stats SA is the national institution responsible for the collection, production and dissemination of official vital statistics in South Africa. With regard to reporting mortality, the legislation requires that a medical doctor completes the death notification form (form BI-1663), providing information on the immediate and underlying causes of death or any antecedent event/cause that might have contributed to the death.

Deaths due to unnatural causes require medico-legal investigations and, for this purpose, autopsies are conducted in government forensic laboratories to ascertain the cause of death. All death notification forms are submitted to the Department of Home Affairs. Stats SA compiles, at the national level, all the death notification information, and codes the causes of death using the 10^{th} revision of the International Classification of Diseases (ICD-10 codes) where mesothelioma is defined using the code C45 (5).

Mesothelioma death is defined as death caused by the development of mesothelioma that has been confirmed by a histopathological test and recorded on the death certificate as the primary or secondary cause of death (33,34).

2.2.2 The National Cancer Registry of South Africa (NCR)

The NCR of the National Health Laboratory Service (NHLS) is a passive pathology-based surveillance system that was established in 1986 (14). It is a pathology and population-based registry that records all incident cancer cases and collects information on mesothelioma cases from pathology-based cancer reports obtained from all public and private laboratories in South Africa. The information provided by the NCR is summarized in Appendix 2.

2.2.3 The Pathology Automation System (PATHAUT)

The PATHAUT database at the National Institute for Occupational Health (NIOH) contains records dating back to 1975 (35) and includes information from autopsy examinations and clinical files (which include brief occupational histories) of deceased people who worked in the South African mining, quarry and foundry industries. These autopsy examinations are performed by the Pathology Division of the NIOH on behalf of the Medical Bureau for Occupational Diseases under the Occupational Diseases in Mines and Works Act of South Africa (Act 78 of 1973). The annual PATHAUT reports provide information on mesothelioma incident and death cases linked to occupational and environmental asbestos exposure.

2.2.4 The Asbestos and Kgalagadi Relief Trusts (ART/KRT)

The ART/KRT are Trusts established in 2003 and 2006, respectively, with the purpose of providing compensation for mesothelioma or other asbestos-related diseases to claimants while alive, or to their families after death, who worked in or lived in the vicinity of specific asbestos mines, and developed mesothelioma or other asbestos-related diseases which were confirmed by diagnostic methods, such as chest X-ray, spirogram, histology and autopsy results (10,36). Cases are identified through both passive and active case-finding. The ART/KRT data are collected from medical records of claimants who developed mesothelioma or other asbestos-related diseases. The hard copies of the medical records are gathered, reviewed and stored at the Cape Town ART/KRT office. The ARTMis (Asbestos Relief Trust Management Information System) database provided data collected from records

of claimants, and other data sources, thereby providing individual demographic and occupational exposure information.

2.3 Data Collation

De-identified data were received from the four pre-cited data sources for the study period 2003 to 2013. Data were collated in Excel or Stata file formats as extracted by the gatekeepers, and processed/cleaned using Stata 14.1. The data sets included information on demographic and occupational characteristics of the deceased as shown in Appendix 2.

2.4 Measurement

The dependent variable of interest was “mesothelioma case” in the NCR data set or “mesothelioma death” in the other three data sets. The dependent variable was a simple aggregated count variable and, as such, only had non-negative integer values.

2.5 Data Processing and Study Variables

The Stats SA, NCR, PATHAUT, and ART/KRT data are administrative data, and were transformed into research data sets in Stata data format (.dta format). More variables were available in the Stats SA data set than in the NCR data set as presented in the list of variables (Appendix 2).

Data cleaning and correction were done using Stata version 14.1 software (StataCorp LP College Station, TX). Inconsistencies and duplicates were checked for in the different data sets using the variables ‘serial number’ for Stats SA, ‘registration number’ for NCR, ‘Pathology number’ for PATHAUT/NIOH, and ‘file number’ for ART/KRT. The geographical mapping of mesothelioma deaths aggregated by province was done using ArcGIS software. Appropriate data management is described in the following sections.

2.5.1 Stats SA data set

Data from Stats SA were received in Excel format. The files contained 50 variables with 2205 observations; 73 cases were excluded because of unspecified or citizenship other than South African.

Only a few variables were useful for the analysis and their processing is presented in Table 2.1. Unknown and unspecified values in categorical variables were combined into one group

labelled “unspecified”. The remaining 2 132 constituted the final study population for the 2003-2013 period.

Table 2.2.1: Study variables in Stats SA data set

Study Variable	Format	Data management process
Death count	Numerical	Variable generated as a count of mesothelioma deaths for each year of study
Year of death	Ordinal	From 2003 to 2013
Age in completed years	Numerical	Defined as age at death. Values corresponding to “999” were converted to missing
Age group 1	Categorical	5-year age group recode from age in continuous completed years
Age group 2	Categorical	10-year age group recoded from the variable "age in completed years" as 1=<20years, 2=20-39 years, 3 =40-59 years, 4=60-74 years, and 5=75+ years
Sex of deceased	Categorical	Recoded as 1=Male 2=Female
Population group	Categorical	Recoded as 1=Black 2=White 3=Indians or Asian 4=colored 5=Unspecified
Population size	Numerical	Variable generated using the mid-year populations of South Africans each year of study
Mid-year provincial population	Numerical	Variable generated using the mid-year populations of South Africans aggregated by sex, province, and race, and age group for each year of study
Smoking status of the deceased	Categorical	Recoded 1=yes 2=No 3=Unspecified
Province of death occurrence	Categorical	Coded as 1=Western Cape, 2=Eastern Cape, 3=Northern Cape, 4=Free State, 5=KwaZulu-Natal, 6=North West 7=Gauteng, 8=Mpumalanga, 9=Limpopo"
Province of residence	Categorical	Coded as 1=Western Cape, 2=Eastern Cape, 3=Northern Cape, 4=Free State, 5=KwaZulu-Natal, 6=North West 7=Gauteng, 8=Mpumalanga, 9=Limpopo"
Occupation group of deceased	Categorical	Recoded as 1=Armed forces/occupations unspecified 2=Legislators/senior officials/managers 3=Professionals 4= Technicians and associate professionals 5=Clerks 6=Service workers, shop and market sales 7=Skilled agricultural and fishery worker 8=Craft and related trade workers 9=Plant and machine operators and assembly 10=Elementary occupations 11=Unspecified

2.5.2 NCR data set

The NCR data set contained 1 242 observations that were included in the analysis. At the time of data collation, data from 2011 to 2013 were not yet available, and there was no information available on citizenship of the cases. The variables used for analysis are summarized in Table 2.2.

Table 2.2: Study variables in NCR data set

Study Variable	Format	Data management process
Age at diagnosis (in years)	Numerical	
Sex	Categorical	Encoded as 1=Male, 2=Female
Population group	Categorical	Encoded as 1=Asian, 2=Black, 3=coloured, 4=Unspecified, 5=White
Year of diagnosis	Discrete	from year 2003 to year 2010
Province of diagnosis	Categorical	Encoded as 1=Eastern Cape, 2=Free State, 3=Gauteng, 4=KwaZulu Natal, 5=Limpopo, 6=Mpumalanga, 7=Northern Cape, 8=North West Province, 9=Western Cape

2.5.3 PATHAUT data set

That PATHAUT data set contained 385 records of mesothelioma death cases from 2003 to 2013; four were excluded because their deaths occurred in the year 2002 despite being recorded in 2003; 381 observations were analyzed. No information on the location of cases was available. The variables shown in Table 2.3 were used in the analysis.

Table 2.3: Study variables in the PATHAUT data set

Study Variable	Format	Data management process
Age at death (in years)	Numerical	
Year of death	Discrete	From 2003 to 2013
Sex	Categorical	Encoded as 1=Female, 2=Male, 3=Unspecified
Population group	Categorical	Encoded as 1=Black, 2=White, 3=colored, 4=Indian, 5=Unspecified

2.5.4 ART/KRT data set

The ART/KRT data set contained 16 543 observations after merging two data sets: one had more variables on occupational information, and the other contained the demographic variables of the claimants. The ARTMis database contains information on all claimants, regardless of disease status. There were 4 067 duplicate observations in in the merged data set; 16 044 were excluded because they were not confirmed mesothelioma cases or because they were non-South Africans. Observations where year of registration was after 2003 but death occurred before 2003, or those where year of registration was after 2013 and death had not occurred by 2013, were excluded, as well as those where the region was recorded as Lesotho, Botswana, Namibia, or Swaziland. The 499 remaining observations were identified as mesothelioma cases and were included in the analysis. The variables in the ART/KRT database are described in Table 2.4.

Table 2.4: Study variables in ART/KRT data set

Study Variables	Format	Data management process
Age at death (in years)	Numerical	
Age at registration (in years)	Numerical	
Age at registration group	Categorical	coded from Age at registration, as 1= 30-39 years, 2=40-49 years, 3=50-59 years, 4=60-69 years, 5=70-79 years, 6=80-89 years, 7=90 years+
Year of registration	Discrete	From 2003 to 2013, extracted from Registration date
Year of death	Discrete	From 2003 to 2013, extracted from date of death
Sex	Categorical	coded as 1=Female, 2=Male
Population group	Categorical	coded as 1=Black, 2=White, 3=colored, 4=Indian, 5=Unspecified
Region	Categorical	coded as 1= Botswana, 2=Eastern Cape, 3=Free State, 4=Gauteng, 5=Kwazulu-Natal,6=Lesotho, 7=Limpopo, 8=Mpumalanga, 9=Namibia, 10=North West, 11=Northern Cape, 12= Swaziland 14=Western Cape, 13=Unknown
Diagnosis type	Categorical	coded as 0=ARD3, 1=ARD4=Meso, 2=No ART compensable, 3=Pending. Only the observations in category Meso=1 were kept for the analysis
Smoking	Categorical	coded as 0=No, 1=Yes, and 2=Unknown
History of Pulmonary TB	Categorical	coded as 0=No, 1=Yes, and 2=Unknown

2.6 Data Analysis

2.6.1 Descriptive analysis

The first objective aimed to determine and compare the number of mesothelioma cases that occurred from 2003 to 2013 in each province. Frequency (n) and percentage (%) tables were used to summarize categorical variable while mean and standard deviation were used to summarize the variable age in all data sets after verifying the assumption of normal distribution. A bar graph was used to visualize the distribution of mesothelioma deaths by 5-year age groups using the Stats SA data set. The second objective aimed to describe and map the age standardized mesothelioma incidence and mortality rates by province, using Stats SA data.

Mid-year population estimates

Official South African mid-year population estimates as reported by Stats SA, were used as the denominator for the calculation of age-specific and age-standardized mortality rates (ASMR). The population estimates are reported, aggregated by sex, age-group, population group, and by province for each year of study, except the 2012 estimates which were obtained using the population growth rate of 1.52 from 2011 to 2012, as follows:

2012 mid-year population estimates = 2011 mid-year population estimate X (100+1.52)/100

Age -specific incidence rates per 100 000

The age-specific incidence rates were calculated by direct method for each year, using the NCR data in Excel (Microsoft Office 2010) for each age group, by dividing the number of mesothelioma incident cases in each 5-year age group by the mid-year population estimates of South Africans, which were then multiplied by 100 000 (37).

$$\textit{Age-specific mortality rate} = \frac{Total\ number\ of\ mesothelioma\ incidence\ in\ a\ specified\ age\ group\ for\ specific\ year}{Mid-year\ population\ of\ the\ specified\ age\ group} \times 100\,000$$

Age-specific mortality rates per 100 000

The age-specific mortality rates were calculated, using Stats SA data, by direct method for each year of study to adjust the crude mortality rates for the differences in population age structure for a 5-year period. They were calculated in Excel (Microsoft Office 2010) for each

age group by dividing the number of mesothelioma deaths in each 5-year age group by the mid-year population estimates of South Africans, which were then multiplied by 100 000 (37)

Age-specific mortality rate =

$$\frac{Total\ number\ of\ mesothelioma\ deaths\ in\ a\ specified\ age\ group\ for\ specific\ year}{Mid-year\ population\ of\ the\ specified\ age\ group} \text{ x } 100\ 000$$

Age-standardized mortality rates (ASMR)

The ASMR were calculated from the age-specific mesothelioma mortality rates to adjust for differences in age groups, race, gender, and the province of death. The ASMR calculation incorporates an adjustment for the difference in population structure applied to the WHO World standard population which is based on the year 2000 population (38). The WHO standard was used to generate estimates comparable to population data of other countries and to maximize the international comparability of published statistics. This process ensures that the mesothelioma mortality estimates are comparable to other population estimates. A table with details of the age-structured World standard population used to calculate the age standardized estimates rates can be found in Appendix 3.

$$\textit{Age Standardized Mortality Rate} = \frac{\Sigma\ Ai\ Wi}{\Sigma\ Wi} \text{ x } 100 \text{ for } i = 1, 2, \ldots, n$$

Where A_i = age specific mortality rate for age group *i*

W_i = World standard population for age group *i and* n = the number of age groups

Average Annual percent change in ASMR

A nonlinear regression analysis was used to examine the trends of the logarithmically-transformed mesothelioma AMSR over the years of study (39). Joined fitted values of AMSR and their 95% confidence intervals were plotted on a line graph. The regression coefficient of "Death year" was used as the beta value in the calculation of average annual percent change (AAPC), using the formula:

$$\boldsymbol{AAPC = (e^{\beta} - 1) \times 100}$$

Spatio-temporal analysis

To delineate the different provincial standardized mortality rates, colour coding was used to show the magnitude of mortality for each year and province, using ARCGIS software. The mortality rates were calculated and classified into six categories; from which categories of low, moderate and high standardized mortality rates per 100 000 populations were derived. To map the mesothelioma ASMR for each province over the years, the Hartebeesthoek94 Datum was used. It is the official geodetic datum for South Africa, using the Gauss Conform Coordinate System (40) which covers the entire country and comprises approximately 29 000 highly visible trigonometrical beacons on mountains, tall buildings and water towers, as well as approximately 20 000 easily accessible town survey marks.

2.6.2 Statistical analysis

The third objective aimed to determine factors associated with mesothelioma mortality rates in South Africa from 2003 to 2013. All hypotheses testing were carried out using a confidence level of 95%. A Poisson regression model could not be used because the equi-dispersion assumption or assumption of equality between the mean and the variance was not met and over-dispersion of the observations (mean ≠ variance) was found (Appendix 4). Therefore, to avoid underestimation of standard errors, the negative binomial regression model was used to identify the factors associated with mesothelioma death in the study population (41).

Unadjusted and adjusted negative binomial regression analyses techniques were used to explore any potential associations of independent variables with 'Mesothelioma death count', the dependent variable of interest. Variables for which the bivariate analysis showed a p-value of 0.20 or less were included in the final multivariable model, and mortality rate ratios were calculated. For the purpose of this study analysis, province of death was used rather than province of residence because they were similar and province of death had fewer missing values (Appendix 5).

Two different negative binomial regression models were fitted. The first model used, as exposure population, the mid-year population estimates aggregated by age group, sex and province of death; the second model used, as exposure population, the mid-year population estimates aggregated by age group, sex and population group. Stats SA does not report

population estimates aggregated by both population group and the province of death, which is the reason that two different models were fitted separately, including either the population group or the province of death. Through backward elimination, the non-significant explanatory variables were removed until a final model was obtained with significant explanatory variables with P-values <0.05. All the results were reported using the mortality rate ratio (MRR) together with their 95% confidence intervals and P-values of association.

The negative binomial regression model, which follows a gamma distribution, was expressed as follows:

$$P(y \mid X) = 1 + \frac{\Gamma(y+\alpha^{-1})}{y!\,\Gamma(\alpha^{-1})} + \left(\frac{\alpha^{-1}}{\alpha^{-1}+\mu}\right)^{\alpha^{-1}} + \left(\frac{\mu}{\alpha^{-1}+\mu}\right)^{y} + \cdots$$

Where "y" represents the outcome of interest (mesothelioma death count) and Mu (μ) represents the mean incidence rate of mesothelioma death per unit of exposure. Alpha is the heterogeneity parameter and represents the extent of overdispersion. When alpha is equal to zero, the model reduces to simple Poisson regression. In this analysis, the likelihood ratio test of alpha was highly significant (P-value <0.001), confirming the appropriateness of using the negative binomial regression analysis method to determine factors associated with mesothelioma deaths.

$$\text{Log (Mesothelioma_Death_count)} = \exp(\text{Intercept} + b_1*\text{var1} + b_2*\text{var2} + b_3*\text{var3} + \ldots)$$

The model goodness of fit chi-square was tested to evaluate the adequacy of the final negative binomial regression model.

2.7 Ethical considerations

This study was approved by the University of the Witwatersrand Human Research Ethics (Medical) Committee (HREC). The authorization letters and the clearance certificate, number M151167, can be found in Appendix 6. Authorization to use the data sets was obtained from each data source gate keeper. The data files were kept anonymised and password protected to ensure confidentiality of the participants' information.

CHAPTER 3 : RESULTS

In this chapter, the results of the secondary analysis of data from 2003 to 2013, obtained from the Statistics of South Africa (Stats SA), the National Cancer Registry of South Africa (NCR), the PATHAUT database, and the Asbestos and Kgalagadi Relief Trusts (ART/KRT) are presented. The demographic and behavioural characteristics of individuals who had malignant mesothelioma and the investigated factors associated with mesothelioma are described. In addition, the main demographic characteristics of the participants, from the four different data sources, are compared. Spatio-temporal mapping of annual mesothelioma age standardized mortality rates are displayed by province. The two models resulting from the negative binomial regression analyses to identify the risk factors associated with mesothelioma death counts, using the Stats SA data set, are presented.

3.1 Mesothelioma incidence (2003-2010)

3.1.1 Demographic characteristics of the NCR study population (2003-2010)

The total number of cases in all the provinces of South Africa recorded in the NCR data set from 2003 to 2010 was 1 242 (average of 155 new cases per year).

Over the study period, 77.8% of mesothelioma cases occurred in males with a sex ratio of 3.5:1 (Table 3.1). The average age at diagnosis was 62.3 years (SD: 11.6), and 86.1% of the cases occurred among those older than 50 years. Most cases occurred in the white and black population groups (48.6% and 31.6%, respectively).

Table 3.1: Demographic characteristics of the NCR study population (mesothelioma cases, 2003-2010)

Characteristic		n	%
Sex	Male	966	77.8
	Female	274	22.1
Age group (years)	<20	1	0.1
	20-29	5	0.4
	30-39	31	2.5
	40-49	126	10.3
	50-59	325	25.6
	60-69	395	32.3
	70-79	255	20.9
	80-89	82	6.7
	90 +	2	0.6
Population group	White	603	48.6
	Black	393	31.6
	Coloured	158	12.7
	Asian	31	2.5
	Unspecified/unknown	57	4.6

N: Frequency; %: Column percentage

The province reporting the highest number of cases was Gauteng (50.8%) and the province with the lowest number of cases reported was Mpumalanga (<1%) (Table 3.2).

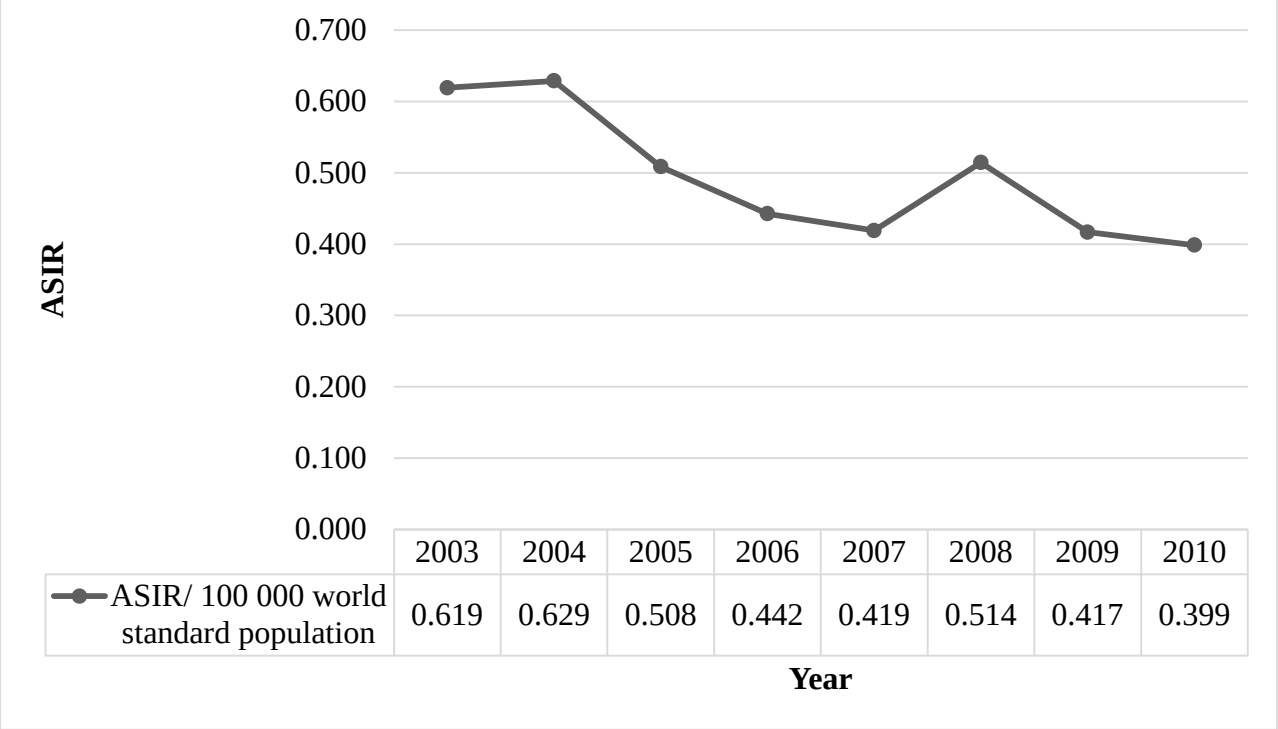
Table 3.2: Frequency distribution of mesothelioma cases per province (source: NCR 2003-2010)

Province	2003		2004		2005		2006		2007		2008		2009		2010		Total	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Gauteng	84	44.2	85	49.7	88	54.7	79	54.5	74	53.2	79	49.1	80	58.0	62	45.3	631	50.8
Western Cape	33	17.4	39	22.8	26	16.2	26	17.9	27	19.4	23	14.3	26	18.8	19	13.9	219	17.6
Free State	38	20.0	24	14.0	20	12.4	20	13.8	11	7.9	15	9.3	5	3.6	11	8.0	144	11.6
Northern Cape	8	4.2	6	3.5	1	0.6	1	0.7	8	5.8	19	11.8	9	6.5	26	19.0	78	6.3
KwaZulu Natal	15	7.9	4	2.3	18	11.2	7	4.8	5	3.6	12	7.5	9	6.5	5	3.7	75	6.0
Eastern Cape	6	3.2	8	4.7	6	3.7	4	2.8	5	3.6	4	2.5	3	2.2	5	3.7	41	3.3
North West	3	1.6	3	1.8	2	1.2	5	3.5	5	3.6	4	2.5	1	0.7	3	2.2	26	2.1
Limpopo	1	0.5	1	0.6	0	0.0	2	1.4	0	0.0	3	1.9	4	2.9	6	4.4	17	1.4
Mpumalanga	2	1.1	1	0.6	0	0.0	1	0.7	4	2.9	2	1.2	1	0.7	0	0	11	0.9
Total	190	100	171	100	161	100	145	100	139	100	161	100	138	100	137	100	1242	100

n: frequency; %: column percentage

3.1.2 Age-standardized mesothelioma incidence rates (2003-2010)

The age-standardized incidence was higher in 2003 (0.619 cases per 100 000 world population), and gradually decreased over the study period (0.399 cases per 100 000 world population in 2010) (Fig. 3.1).



	2003	2004	2005	2006	2007	2008	2009	2010
ASIR/ 100 000 world standard population	0.619	0.629	0.508	0.442	0.419	0.514	0.417	0.399

Figure 3.1: Mesothelioma ASIR per 100 000 World population

A table showing details of the mesothelioma AISR for each age group can be found in Appendix 7.

3.2 Mesothelioma mortality (2003-2013)

3.2.1 Description of the Stats SA study population

3.2.1.1 Socio-demographic characteristics

According to this data set, 2 132 deaths occurred due to mesothelioma in South Africa from 2003 to 2013. Overall, the number of mesothelioma deaths was predominantly high in males (76.6%) with a sex ratio of 3.3:1. The average age at death was 65.1 years (±12.15), with 89.4% of mesothelioma deaths occurring among those older than 50 years (Appendix 8). While the maximum age at death was recorded to have occurred in a 97 year-old person, two cases were reported to have occurred in children under 5 years of age, one of them dying just

five days after birth and the second at 2 years. The proportion of mesothelioma deaths was higher in the 65-70 years age group (16.1%) (Appendix8).

The highest proportion of mesothelioma cases occurred in Whites (49.3%) and Blacks (23.2%) (Table 3.3). A substantial proportion of mesothelioma cases occurred among married individuals (49.3%) while approximately 15% of cases occurred among those who never married.

3. 2.1.2 Frequency distribution of mesothelioma deaths per province using Stats SA data

With an average of 194 cases per year, the highest number of mesothelioma deaths during this period was reported in the Gauteng Province (29.8% of the total cases in South Africa) and the lowest numbers were reported in Mpumalanga and Limpopo Provinces (~3% of the total cases in each). A cumulative proportion of 69.4% of all cases occurred in three of the nine provinces (Gauteng, Northern Cape, and Western Cape provinces) (Table 3.4).

The highest number of cases in the country was reported in 2004 (213 cases) and the lowest number was reported in 2008 (167 cases**).**

Although education level was not available for 57.1% of cases, 26.2% of mesothelioma death cases occurred among individuals with secondary education and 6.89% occurred in tertiary educated individuals. Among the cases recorded, 53.8% had an unknown smoking status and 13.4% were reported to have been smoking up to five years before death.

Table 3.3: Demographic characteristics of mesothelioma deaths in South Africa (source: Stats SA2003 to 2013

Characteristics		n	%
Sex	Male	1 634	76.6
	Female	497	4
Age (Years)	<20	2	0.1
	20-29	13	0.6
	30-39	28	1.3
	40-49	183	8.6
	50-59	426	20
	60-69	664	31.1
	70-79	571	26.8
	80-89	229	10.7
	90+	15	0.7
	Unspecified	1	0.1
Population group	White	1050	49.3
	Black	495	23.2
	Coloured	184	8.6
	Indian/Asian	18	0.8
	Unspecified	385	18.1
Smoker 5 years before death	No	700	13.4
	Yes	285	32.8
	Unspecified	1 147	53.8
Occupation	Armed forces/occupations unspecified	1 119	52.5
	Craft and related trade workers	95	4.4
	Professionals	86	3.8
	Elementary occupations	57	2.7
	Legislators/senior officials/managers	54	2.5
	Technicians and associate professionals	49	2.3
	Plant and machine operators and assembly	37	1.7
	Clerks	25	1.2
	Skilled agricultural and fishery worker	21	1
	Service workers, shop and market sales	18	0.8
	Unspecified	577	27.1

n: frequency; %: column percentage

Table 3.4: Frequency distribution of mesothelioma cases per province (source: Stats SA 2003-2013)

Province of death[1]	2003		2004		2005		2006		2007		2008		2009		2010		2011		2012		2013		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Gauteng	54	28.1	55	25.8	54	31.4	61	27.6	61	34.7	51	30.5	66	34.2	63	31.5	54	26.3	54	27.1	62	32.0	635	29.8
Northern Cape	31	16.2	39	18.3	37	21.5	53	24.0	45	25.6	32	19.2	35	18.1	44	22.0	37	18.1	49	24.6	40	20.6	442	20.7
Western Cape	40	20.8	50	23.5	31	18.0	35	15.8	22	12.5	42	25.2	36	18.7	45	22.5	42	20.5	32	16.1	27	13.9	402	18.9
North West	22	11.5	18	8.5	14	8.1	17	7.7	4	2.3	6	3.6	19	9.8	11	5.5	16	7.8	13	6.5	11	5.7	151	7.1
KwaZulu-Natal	12	6.3	15	7.0	9	5.2	20	9.1	14	8.0	8	4.8	9	4.7	14	7.0	13	6.3	19	9.6	17	8.8	150	7.0
Free State	10	5.2	15	7.0	15	8.7	10	4.5	9	5.1	10	6.0	8	4.2	6	3.0	11	5.4	9	4.5	15	7.7	118	5.5
Eastern Cape	11	5.7	5	2.4	4	2.3	10	4.5	12	6.8	8	4.8	10	5.2	11	5.5	16	7.8	10	5.0	7	3.6	104	4.9
Limpopo	6	3.1	10	2.8	2	3.5	8	3.2	2	4.0	7	1.8	6	2.1	3	1.5	6	4.9	7	3.0	8	3.6	65	3.1
Mpumalanga	6	3.1	6	4.7	6	1.2	7	3.6	7	1.1	3	4.2	4	3.1	3	1.5	10	2.9	6	3.5	7	4.1	65	3.1
Total	**192**	**100**	**213**	**100**	**172**	**100**	**221**	**100**	**176**	**100**	**167**	**100**	**193**	**100**	**200**	**100**	**205**	**100**	**199**	**100**	**194**	**100**	**2 132**	**100**

n: frequency; %: column percentage

[1] Province of death here is probably the province where death was reported and not necessarily where mesothelioma was diagnosed

3.2.2 Description of the PATHAUT study population (2003-2013)

3.2.2.1 Demographic characteristics

Table 3.5: Demographic characteristics of mesothelioma cases (source: PATHAUT 2003-2013) (N = 381)

Characteristics		n	%
Sex	Male	311	81.6
	Female	60	15.8
	Unspecified	10	2.6
Age group	<40 years	6	1.6
	40-49 years	39	10.2
	50-59 years	101	26.5
	60-69 years	110	28.9
	70-79 years	85	22.3
	80-89 years	22	5.8
	90+ years	4	1.1
	Unspecified	14	3.7
Population group	Black	229	60.1
	White	132	34.7
	Coloured	10	2.6
	Indian	8	2.1
	Unspecified	2	0.5

n: frequency; %: column percentage

There were 381 cases of mesothelioma recorded in the PATHAUT data set from 2003 to 2013 in South Africa. Most mesothelioma cases recorded were of males (n=311; 81.6%) with a sex ratio of 5.2:1. The reported cases were predominantly among Blacks (60.1%) and Whites (34.5) (Table 3.5). The average age at death was 62.9 years (SD: 11) with 84.5% being older than 50 years. The youngest age at death was 35 years and the oldest was 98 years.

3.2.2.2 Frequency distribution of mesothelioma deaths (PATHAUT 2003-2013)

Over the 11-year study period, the average number of mesothelioma cases recorded was 35 per year, with the lowest documented in 2007 (n=22) and the highest in 2008 (n=48), as presented in Table 3.6.

Table 3.6: Frequency distribution of mesothelioma deaths (Source: PATHAUT 2003-2013)

Year of death	Female		Male		Unspecified		Total
	n	**%**	**n**	**%**	**n**	**%**	**n**
2003	2	6.1	31	93.9	0	0	33
2004	4	16	21	84	0	0	25
2005	9	22	32	78.1	0	0	41
2006	6	26.1	17	73.9	0	0	23
2007	5	22.7	17	77.3	0	0	22
2008	7	14.6	36	75	5	10.4	48
2009	2	5.1	35	89.7	2	5.1	39
2010	4	12.9	27	87.1	0	0	31
2011	5	14.2	27	77.1	3	8.6	35
2012	11	24.4	34	75.6	0	0	45
2013	5	12.8	34	87.2	0	0	39
Total	**60**	**15.8**	**311**	**81.6**	**10**	**2.6**	**381**

n: Frequency; %; column percentage

3.2.3 Description of the ART/KRT study population

3.2.3.1 Demographic characteristics

Table 3.7: Socio-demographic characteristics of mesothelioma cases (source: ART/KRT 2003-2013)

Characteristic		N=499	%
Sex	Male	363	72.8
	Female	136	27.3
Age group (years)	30-39	4	0.8
	40-49	94	18.8
	50-59	170	34.1
	60-69	142	28.5
	70-79	70	14.0
	80-89	17	3.4
	90+	2	0.4
Smoking history	No	416	83.4
	Yes	75	15.0
	Unknown	8	1.6
Pulmonary TB history	No	474	95.0
	Yes	17	3.4
	Unknown	8	1.6

The total number of mesothelioma cases recorded from 2003 to 2013 in the ART/KRT data set was 499. More males were registered during the study period (72.8%), with a male to female ratio of 2.67:1 (Table 3.7).

The average age at registration was 59.26 years (±10.6), ranging from 33 years to 98 years. Furthermore, 80.4 % of cases were older than 50 years. Approximately 15% of the registered cases had a smoking history and 3.4% of the cases had a pulmonary tuberculosis history (Table 3.7).

3.2.3.2 Frequency and demographic characteristics of mesothelioma cases in South Africa from 2003-2013 using the ART/KRT data set

As shown in Table 3.8, the most cases that were reported were from the Northern Cape Province (66.7%); the Mpumalanga and Limpopo provinces had the fewest (< 1% each). The highest numbers of diagnosed mesothelioma cases were recorded in 2004 (75) and 2005 (80).

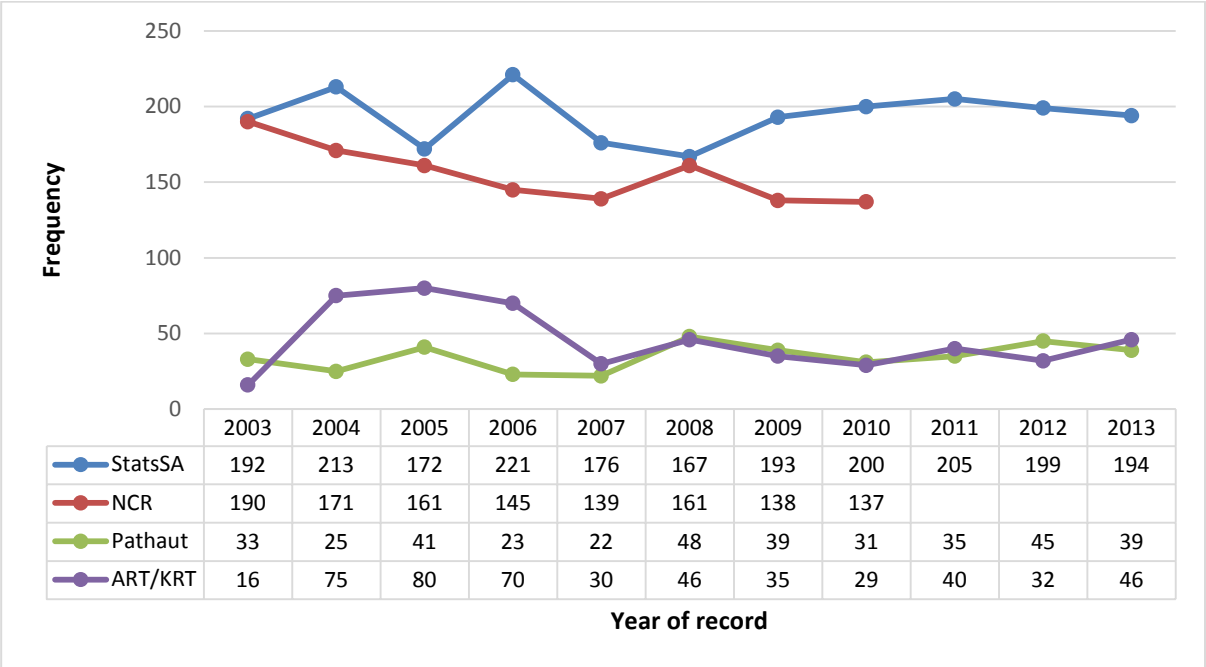
Table 3.8: Frequency distribution of mesothelioma cases per province (source: ART/KRT 2003 to 2013)

Province	2003		2004		2005		2006		2007		2008		2009		2010		2011		2012		2013		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Northern Cape	5	31.3	56	74.7	64	80.0	46	65.7	15	50.0	30	65.2	23	65.7	18	62.1	30	75.0	22	68.8	24	52.2	333	66.7
North West	4	25.0	9	12.0	7	8.8	12	17.1	8	26.7	2	4.4	3	8.6	5	17.2	0	0.0	3	9.4	4	8.7	57	11.4
Gauteng	5	31.3	4	5.3	4	5.0	4	5.7	4	13.3	0	13.0	4	11.4	3	10.3	5	12.5	4	12.5	9	19.6	52	10.4
Western Cape	1	6.3	2	2.7	0	0.0	4	5.7	2	6.7	3	6.5	1	2.9	1	3.5	2	5.0	0	0.0	2	4.4	18	3.6
Free State	1	6.3	1	1.3	2	2.5	1	1.4	1	3.3	6	0.0	1	2.9	1	3.5	1	2.5	0	0.0	2	4.4	11	2.2
Kwazulu-Natal	0	0.0	1	1.3	2	2.5	2	2.9	0	0.0	2	8.7	1	2.9	0	0.0	0	0.0	1	3.1	3	6.5	14	2.8
Eastern Cape	0	0.0	0	0.0	1	1.3	0	0.0	0	0.0	1	2.2	0	0.0	0	0.0	2	5.0	1	3.1	0	0.0	5	1.0
Limpopo	0	0.0	1	1.3	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9	0	0.0	0	0.0	0	0.0	1	2.2	3	0.6
Mpumalanga	0	0.0	1	1.3	0	0.0	0	0.0	0	0.0	46	0.0	0	0.0	1	3.5	0	0.0	1	3.1	0	0.0	3	0.6
Unknown	0	0.0	0	0.0	0	0.0	1	1.4	0	0.0	0	0.0	1	2.9	0	0.0	0	0.0	0	0.0	1	2.2	3	0.6
Total	16	100	75	100	80	100	70	100	30	100	46	100	35	100	29	100	40	100	32	100	46	100	499	100

n: Frequency; %: column percentage

3.2.4 Summary figures of mesothelioma in South Africa using the four data repositories

During the 2003 to 2013 period, the trend of mesothelioma cases recorded in the Stats SA data was relatively stable, while numbers declined gradually in the NCR and the ART/KRT data sets. Conversely, there was a slight increase in the number of mesothelioma cases recorded in the PATHAUT database over the study period, as shown by the dotted linear trend lines (Figure 3.2). Of the four data sets used, the most mesothelioma cases were reported in the Stats SA data set; these are the data that were used in the risk factors analyses of all the variables and mesothelioma mortality rate.



	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
StatsSA	192	213	172	221	176	167	193	200	205	199	194
NCR	190	171	161	145	139	161	138	137			
Pathaut	33	25	41	23	22	48	39	31	35	45	39
ART/KRT	16	75	80	70	30	46	35	29	40	32	46

Figure 3.2: Trends in frequencies of mesothelioma cases among South Africans recorded by different data sources from 2003 to 2013

Table 3.9 summarises the demographic characteristics of mesothelioma cases as reported by all the data sources. Across all the data sources, there was consistency in higher proportions of males than females. In the Stats SA and NCR data sets, most of the mesothelioma cases were white as opposed to the PATHAUT data set, where most of the cases reported were black. In the ART/KRT data set, population group was not recorded.

Table 3.9: Summary table of demographic characteristics

Characteristic		Data sources							
		Stats (N=2132)		SA NCR (N=1242)		PATHAUT (N=381)		ART/KRT (499)	
		n	%	n	%	n	%	n	%
Sex	Male	1634	76.6	966	77.8	309	83.7	363	72.8
	Female	497	23.3	274	22.1	60	16.3	136	27.3
Race	White	1050	49.3	603	48.6	132	34.8	*	*
	Black	495	23.3	393	31.6	229	60.4	*	*
	Coloured	184	8.6	158	12.7	10	2.6	*	*
	Indian/Asian	18	0.8	31	2.5	8	2.1	*	*
	Unspecified	385	18.1	57	4.6			*	*
Mean age ± SD (years)	Female	65.5 ± 13.2		62.56 ± 12		65.1 ± 11.7		62.99 ± 11.5	
	Male	65.1 ± 11.6		62.23 ± 11.4		62.4 ± 11.1		59.76 ± 10.6	
	All	65.2 ± 12		62.3 ± 11.6		62.9 ± 11.2		60.59 ± 0.5	

*unspecified; n: frequency; %: column percentage

3.3 Age-standardized mortality rates of mesothelioma

3.3.1 Average Annual Percent Change in Mesothelioma ASMR

Figure 3.3 presents the calculated mesothelioma Age-Standardized Mortality rates in the world population. The figure shows that, from 2003 to 2004, there was an increase in the mesothelioma ASMR, from 0.63 to 0.83 cases per 100 000 world population, before dropping in 2005 (0.56/100 000 world population). From 2007 to 2011, there was a slight increase in the ASMR from 0.55 to 0.63/100 000 world population. From 2011 to 2013, a decreasing trend was observed from 0.63 to 0.57 mesothelioma cases per 100 000 world population.

When using the log transformation of the ASMR, the AAPC is -1.65% (95% CI: -1.8%; -1.5%) ($P<0.001$) showing that there was a significant decrease in the trend of annual rate of mesothelioma deaths in the country from 2003 to 2013 ($P<0.001$).

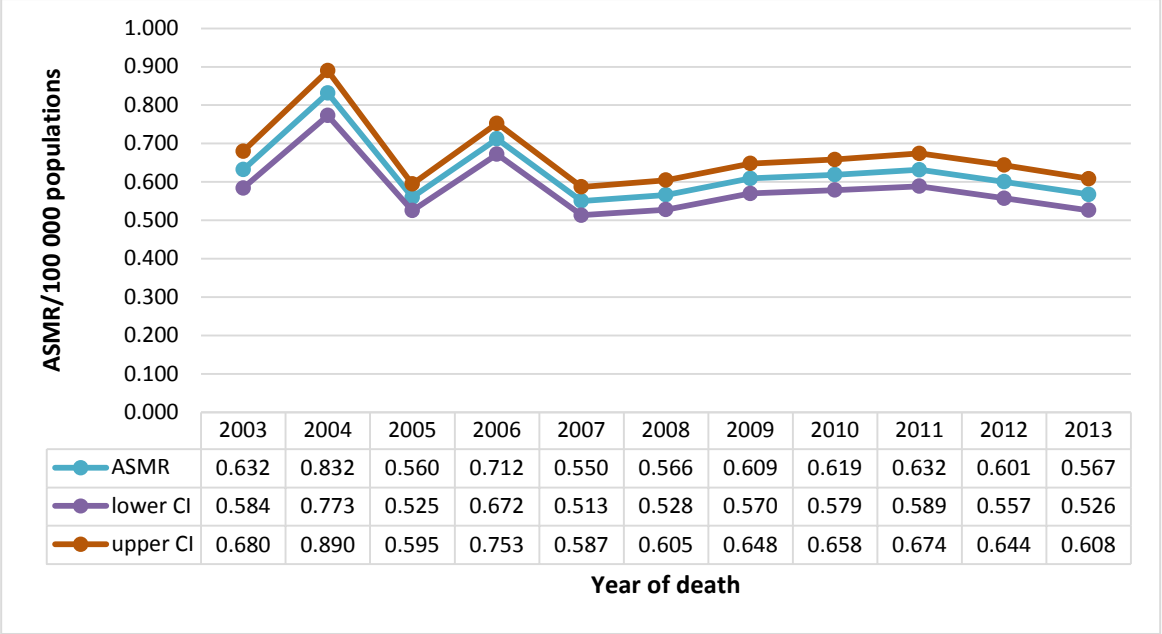


Figure 3.3: Mesothelioma ASMR per 100 000 World standard populations (source: Stats SA)

Table 3.10: Annual Crude and Age Standardized Mortality Rates of mesothelioma in South Africa (2003-2013)

Year	Mid-year Population	Cases	CDR/100 000[2]	ASMR/100 000[3]
2003	46 429 823	191	0.4114	0.6322
2004	46 586 607	213	0.4572	0.8316
2005	46 888 200	172	0.3668	0.5600
2006	47 390 800	221	0.4663	0.7123
2007	47 850 700	176	0.3678	0.5502
2008	48 687 000	167	0.3430	0.5662
2009	49 320 500	193	0.3913	0.6090
2010	49 991 300	200	0.4001	0.6186
2011	50 586 757	205	0.4052	0.6316
2012	52 506 515	199	0.3790	0.6005
2013	52 981 991	194	0.3662	0.5673

[2] Crude death rate per 100 000 World standard population
[3] Age standardized mortality rate per 100 000 World standard population

3.3.2 Trends in ASMR of mesothelioma by age category

Across the 11 years of study, there was a consistent increasing trend in the mesothelioma ASMR from age 30 up, reaching a peak at around age 60 to 70 years (Figure 3.4). A detailed table of the mesothelioma ASMR for each age group can be found in Appendix 9.

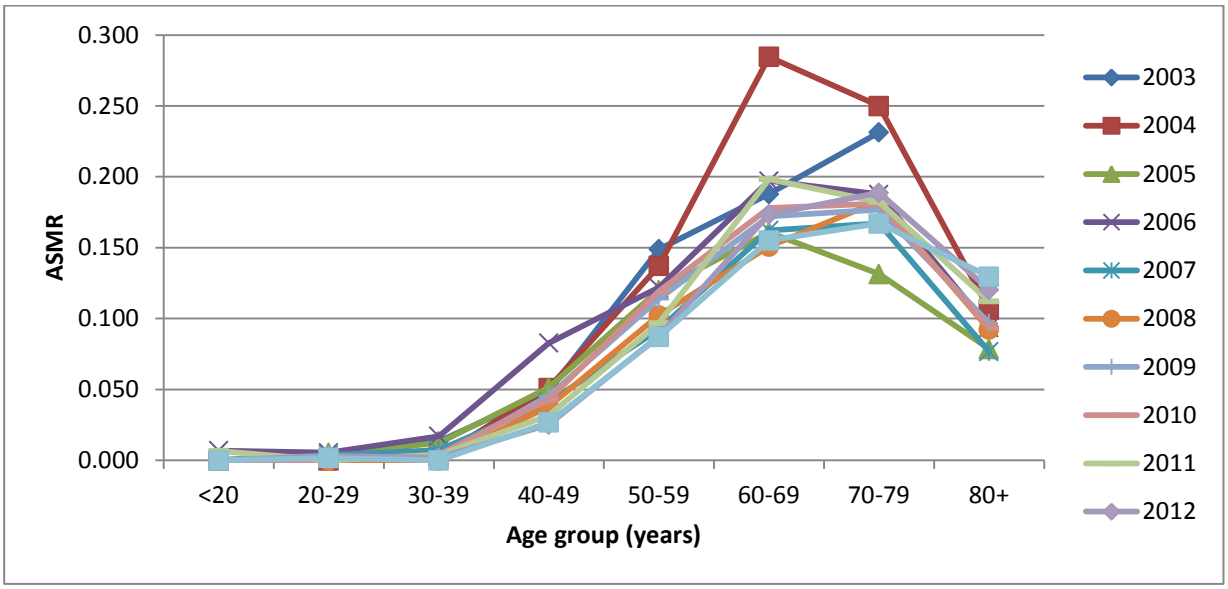


Figure 3.4: Distribution of Annual Mesothelioma ASMR by age group (source: Stats SA 2003- 2013)

3.4 Temporo-spatial analysis of mesothelioma mortality rates in South Africa (2003-2013)

Figure 3.5 and Appendix 10 are the summative graphical presentations of the ASMR per 100 000 World standard population (WHO 2011) of mesothelioma from 2003-2013, by province. There are three main provinces of interest that correspond to the spatial-temporal summary shown in Figure 3.5. To assess the extent of the mesothelioma mortality, the age-standardized mortality deaths were compared by province to show where the greatest burden was.

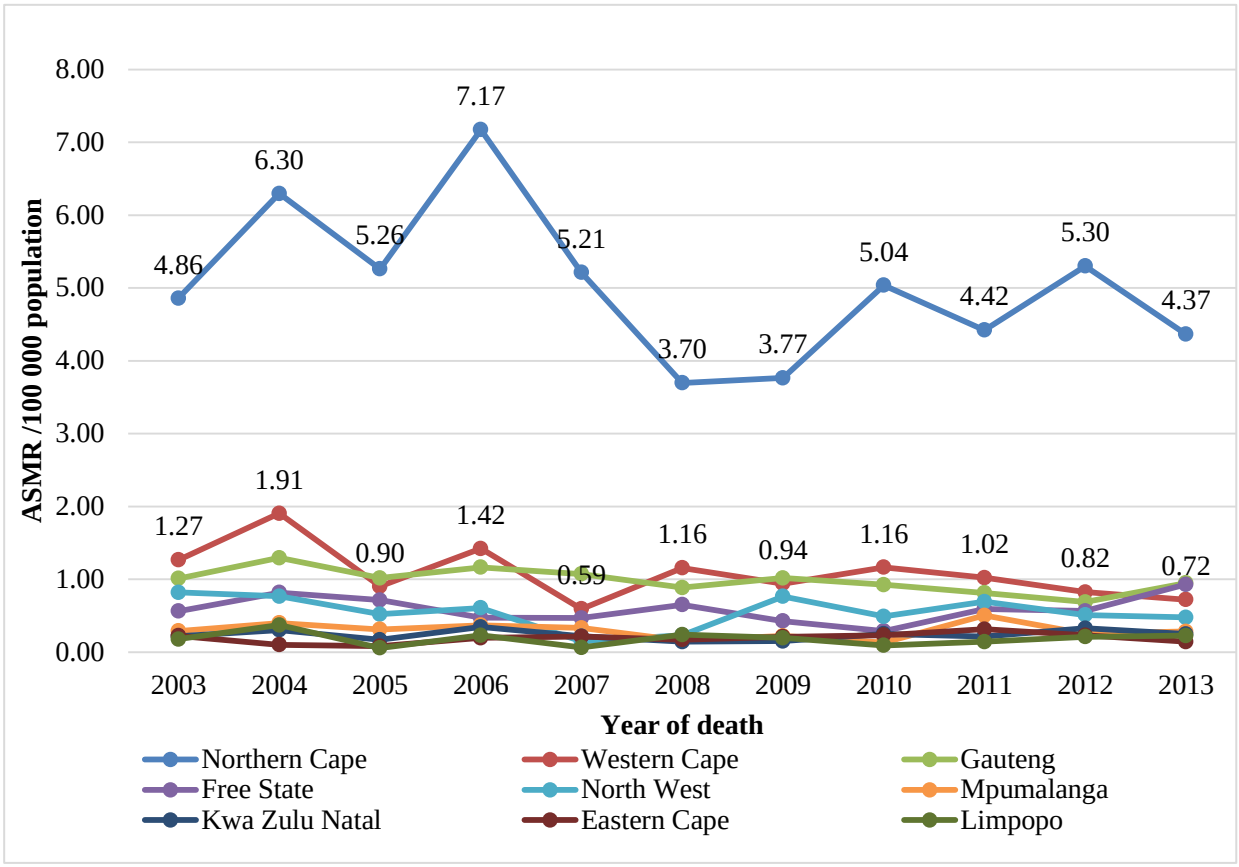


Figure 3.5: Annual Mesothelioma ASMR by Province (Stats SA, 2003-2013)

According to the standardized mortality rate analysis using spatial, temporal mapping and graphs, from 2003 to 2013, the Northern Cape had the highest reported mesothelioma mortality rate. Over the 11 years of observation, there was an average of 3.5 to 7 deaths per 100 000 population reported in the Northern Cape. The Western Cape and Gauteng also both reported a notably higher standardized mortality rate of 1 to 3 cases per 100 000 population in the years 2003, 2004, 2005 and 2006. In the Stats SA database, the results show that a cumulative proportion of over 69% of all cases were reportedly from these three provinces which also show the highest age standardized mortality rates. Similarly, the lowest age-standardized mortality rates were reported from Mpumalanga, Limpopo, Kwa-Zulu Natal and the Eastern Cape which also have the lowest mortality rates according to the Stats SA data.

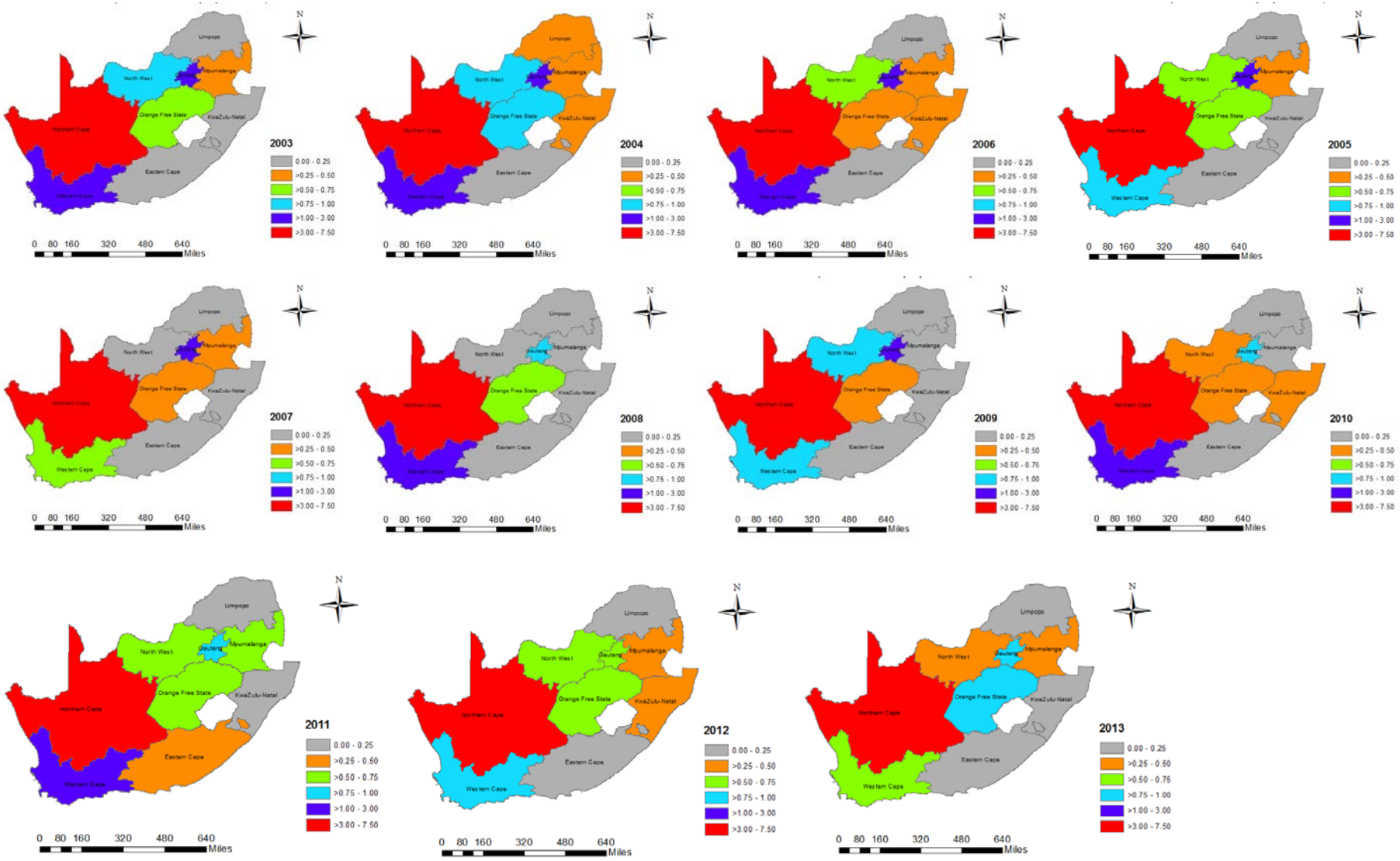


Figure 3.6: Temporal and spatial analysis of mesothelioma age-standardized mortality rates in South Africa (2003-2013, Stats SA data)

3.4.1 Provinces with high standardized mortality rates

The high standardized mortality rates were categorized as mortality rates >1 to 3 per 100 000 standard population (purple colour code) and >3 to 7.5 per 100 000 standard population (red color code) (Figure 3.6). Over the 11 years, the Northern Cape had the highest standardized mortality rates of over 3 to 7.5 per 100 000 standard population. This high standardized mortality rate was observed consistently in all the years (Appendix 11).

The other provinces that also showed high mortality rates were the Western Cape and Gauteng. The Western Cape had mortality rates of greater than 1 - 3 per 100 000 standard population in the years 2003-4, 2006, 2008 and 2010-11. In the alternate years (2005, 2007, 2009, 2012 and 2013) the Western Cape observed low to moderate standardized mortality rates. The Gauteng observed high standardized mortality rates of more than 1 - 3 per 100 000 population in the years 2003-2007 and 2009. Similarly, in the other years (2008, 2010, 2011, 2012 and 2013) Gauteng observed low (<0.05 per 100 000) to moderate (>0.05-1 per 100 000) standardized mortality rates.

3.4.2 Provinces with moderate and low age standardized mortality rates

From 2003, the North-West province had a moderate standardized mortality rate of mesothelioma with 0.5 to 1 per 100 000 standard population until 2006. A significant decrease was observed in the year 2007 and 2008, from 0.5 to 1 per 100 000 to 0 to 0.25 per 100 000 standard population (Appendix 11). Despite a slight increase in moderate mortality rates in 2009, 2011 and 2012, the remaining years had low mortality rates of less than 0.5 per 100 000 standard population. The Free State also observed moderate to low mortality rate fluctuations over the years with the majority of the years showing moderate mortality rates.

Mpumalanga is the only other province that experienced an increase in mortality rates from low to moderate in 2011. The Eastern Cape, Kwa-Zulu Natal, Limpopo and Mpumalanga (except for 2011) reported consistently low standardized mortality rates, with the only fluctuations being from less than 0.25 to 0.25 to 0.5 per 100 000 standard population (Figure 3.6).

3.5 Factors associated with mesothelioma mortality in South Africa (2003-2013)

3.5.1 Negative Binomial Regression Analysis Model 1[4]

In Table 3.11, the unadjusted MRR and adjusted MRR of Model 1 are presented. Model 1 adjusted for age, sex and province of death. The objective of the regression analysis was to identify risk factors for mesothelioma, hence adjusting for all the variables was appropriate as it allowed for the identification of variables that remained independently significantly associated with mesothelioma. A complete table with the results of the unadjusted negative binomial regression analysis can be found in Appendix 12.

Table 3.11: Unadjusted MRR and adjusted MRR of Model 1

		Unadjusted MRR*	P-value	95% CI		Adjusted MRR*	P-value	95% CI	
Age category (years)	**<40**	**1(base)**				**1(base)**			
	40-59	2.257	<0.001	1.98	2.656	1.904	<0.001	1.783	2.033
	60-74	6.480	<0.001	5.553	7.561	5.863	<0.001	5.498	6.252
	75+	26.174	<0.001	22.337	30.671	24.564	<0.001	22.950	26.292
Sex	**Female**	**1 (base)**				**1 (base)**			
	Male	1.163	0.400	1.007	1.342	1.304	<0.001	1.272	1.337
Province of death	**Western Cape**	**1 (base)**				**1 (base)**			
	Eastern Cape	0.681	<0.001	0.552	0.840	0.806	<0.001	0.763	0.852
	Northern Cape	3.520	<0.001	3.185	3.891	4.920	<0.001	4.797	5.047
	Free State	1.434	<0.001	1.212	1.696	2.024	<0.001	1.948	2.102
	KwaZulu-Natal	0.504	<0.001	0.411	0.617	0.674	<0.001	0.651	0.698
	North West	0.961	0.544	0.843	1.094	1.566	<0.001	1.517	1.617
	Gauteng	0.420	<0.001	0.373	0.474	0.545	<0.001	0.531	0.559
	Mpumalanga	1.197	0.082	0.977	1.465	1.894	<0.001	1.804	1.988
	Limpopo	1.059	0.618	0.846	1.326	1.264	<0.001	1.141	1.401

*MRR=Mortality rate ratio; CI confidence interval

[4] The Stata output of Model 1 adjusted negative binomial regression analysis can be found in Appendix 13 and the post-estimation test of fit in Appendix 14

3.5.1.1 Age

Overwhelming evidence of an association between age and mesothelioma deaths was found in this study (P<0.001), after adjusting for sex and province of death. An exponential increase in mesothelioma mortality rate ratio (MRR) as age increased was observed when compared to the MRR of people in the <40 years category, increasing from 1.9 to 24.5 times the mortality rate of mesothelioma in people aged <40 years, with the highest MRR observed in those aged over 75 years (Table 3.11).

3.5.1.2 Sex

There was no association between sex and mesothelioma deaths in the unadjusted model (MRR=1.16, p>0.05) as shown in Table 3.11. After adjusting for age and province of death, the MRR of mesothelioma deaths in males was 1.3 times that in females (P<0.001).

3.5.1.3 Province of Death

After adjusting for age and sex in Model 1, there was convincing evidence of an association between the province of death and mesothelioma deaths (P<0.001). Using the Western Cape as the reference base, the Northern Cape and Free State provinces had the highest mesothelioma mortality rates, five and two times greater, respectively, while the Gauteng's rate was 0.55 times that of the Western Cape (Table 3.11).

3.5.2 Negative Binomial Regression Analysis Model 2[5]

In Model 2, two variables (age and sex) which were included in the unadjusted and adjusted negative binomial regression Model 1 were also included but the province was excluded. In Model 2, there was an addition of a population group variable (Table 3.12).

[5] The Stata output of Model 2 adjusted negative binomial regression analysis can be found in Appendix 15 and the post-estimation test of fit in Appendix 16

Table 3.12: Negative Binomial Regression Analysis Model 2

		Unadjusted MRR*	P-value	95% CI		Adjusted MRR*	P-value	95% CI	
Age category (years)	**<40**	**1(base)**				**1(base)**			
	40-59	2.257	<0.001	1.98	2.656	2.079	<0.001	1.862	2.320
	60-74	6.480	<0.001	5.553	7.561	5.954	<0.001	5.313	6.673
	75+	26.174	<0.001	22.337	30.671	20.583	<0.001	18.287	23.168
Sex	**Female**	**1 (base)**				**1 (base)**			
	Male	1.143	0.130	0.962	1.358	1.305	<0.001	1.274	1.338
Population Group	**Black**	**1 (base)**				**1 (base)**			
	White	7.140	<0.001	6.632	7.688	3.087	<0.001	2.994	3.182
	Indian/Asian	34.037	<0.001	23.567	49.157	18.788	<0.001	17.416	20.268
	Coloured	7.615	<0.001	6.799	8.529	7.016	<0.001	6.767	7.274

MRR= Mortality Rate Ratio; CI= confidence interval

3.6.2.1 Age

When adjusting for sex and population group in Model 2, a similar exponential increase in the mesothelioma MRR in different age groups was observed, from 2 to 21 times the MRR in those under 40 years, with the highest MRR being in those older than 75 years (Table 3.12).

3.6.2.2 Sex

As for Model 1, there was no statistical significant association between sex and mesothelioma deaths in the unadjusted Model 2 (MRR=1.14 P=0.13) as presented in Table 3.12. However, when holding the other variables constant (i.e. age category and population group), the MRR of mesothelioma in males was 1.3 times that in females (P<0.05), which is similar to what was observed in Model 1 (Table 3.12).

3.6.2.3 Population group

There was also a statistically significant association between population group (race) and mesothelioma deaths when adjusting for age and sex. Using the Black group as a reference, the White, Indian/Asian, and Coloured groups had greater mortality rates of mesothelioma deaths, with respective MRRs of 3.1, 18.8 and 7 (P<0.001) (Table 3.12).

CHAPTER 4 : DISCUSSION

The aim of this study was to determine the burden of mesothelioma in South Africa from 2003 to 2013, using available data from four different but routinely collected data sources, and to calculate the age standardized mortality rates for each province in the country. This chapter discusses the results of this research and compares them with previous publications, before expanding on the strengths and limitations.

4.1 Comparison with others studies

From the analysis regarding age standardized mortality rates, South Africa has, on average, a rate of 0.55 to 0.66 mesothelioma deaths per 100 000 World standard population. This is similar to the global rate provided by the World Health Organization (33,34) on country-specific age standardized mortality rates, as reported by Delgermaa et al. (5).

4.1.1 Age and mesothelioma

The South African population is constituted of multiracial communities disseminated across the country, but which are predominantly black at 80.2% (South African National Census 2011, Stats SA). The most recent South African census which was held in 2011, estimated the median age of the population as 25 years, and reported that the overall life expectancy at birth had increased from 52.1 years in 2003 to 59.6 years in 2007 (Stats SA, 2013 report) due, in part, to the impact of Antiretroviral therapy introduction in the country (42).

The mean age at death of individuals dying from mesothelioma was similar in all the four data sources, i.e. 60-63 years, with the majority of cases (80%) reported in patients aged 50 years and older. This is consistent with findings from a previous study which showed that the average age at death of people dying from mesothelioma in South Africa is lower when compared to other developed countries (5). According to Braun and Kisting (2006), there was not much empirical documentation on exposure to asbestos levels in South Africa until the late 1940s. However, they alleged that, according to descriptions of the few available studies about asbestos mining and milling in South Africa, there was high exposure to asbestos fibre at much younger ages in South Africa than anywhere else in the world (7). There are reports of children being used to stamp down the asbestos fibres in sacks (7,43). This could explain

why people with mesothelioma in South Africa die at a younger age than the average age at death of 70 years that is globally reported (5).

Kielkowski and colleagues suggested that the high rate of comorbidities such as HIV infection, tuberculosis, and other opportunistic infections is also a possible reason for early deaths in the South African population. However, co-morbid factors were not explored in this study because such information was not available from the data sources.

4.1.2 Mesothelioma in children

An interesting observation from the Stats SA data was two cases of mesothelioma deaths in children under the age of five: one from KwaZulu Natal who died at the age of 2 years in 2006, and the other one who died just a few days after birth in the Eastern Cape in 2011. These two cases need to be investigated further to rule out any error of the reported observations. It is extremely unlikely for a new-born to have mesothelioma because of the long latency period and relatively slow growth of the tumour. However, few studies have shown that there is a considerable risk of developing mesothelioma in later life if exposed to asbestos early in life, as a child (44–46). Many cases of mesothelioma in children have been identified in the United States, Austria, Brazil, and other countries (47–49). In Japan, Nishioka and his team reported a case of congenital malignant peritoneal mesothelioma diagnosed in a 16-day-old baby (50). There is, however, no conclusive evidence to verify the role of possible prenatal environmental asbestos exposures. There is need to investigate the level of environmental exposure or even occupational exposure and its effect during pregnancy and after birth.

4.1.3 Sex and mesothelioma

Consistently across all the data sets, there were at least three times as many male cases of mesothelioma as female cases. This ratio is similar to that reported in studies from many other countries, and corroborates the findings of other studies conducted in South African populations. One of the reasons suggested by Kielkowski and her colleagues (2011) in an analysis of the mortality trends from 1995 to 2007 was that males had higher occupational and environmental asbestos exposures than females. The regression analysis has shown that men had a 1.3 times higher risk rate of dying of mesothelioma when compared to women. This is in line with what is widely accepted, as women have longer life expectancies than

men; even in the case of mesothelioma, there is evidence of a difference in the mortality patterns between males and females, as men died sooner than women after diagnosis.

4.1.4 Race and mesothelioma

There is an interesting trend in the distribution of mesothelioma cases by race. In the Stats SA and NCR data, there were more cases of mesothelioma amongst the white population from 2003 to 2013. The Stats SA data are more representative of the population and give a true reflection of the population level burden. The dominance of reported mesothelioma in the white population could be explained by either the competing causes of death, such as HIV/AIDS and TB, which lowered life expectancy among Blacks compared to Whites (51,52), and/or the racial differences relative to access and utilisation of health care services which still happen post-Apartheid (53).

Data from other similar studies in South Africa also reported more mesothelioma cases amongst the white population compared to the black population (52). There is a well-documented historical pattern of migrant black workers from across southern Africa, which could explain the fewer cases of mesothelioma in Black people in South Africa; there were many mine workers that came from and returned to Lesotho, Botswana, Swaziland and Mozambique (54). The in-migration from rural areas to mining towns, the 'homeland system' put in place during the apartheid regime, as well as the migrant workers from neighbouring countries who were likely to have moved back to their homes with the disease and died there (7) without being diagnosed, are factors that could explain the lower number of cases reported amongst the black population (55). Since the diagnosis of mesothelioma is mostly post-mortem, these cases could have been missed or misdiagnosed in the majority of the black population because no autopsies were performed on them (5).

Data from the PATHAUT database, however, showed that there were more black individuals with mesothelioma in the study period. The PATHAUT information provided data from autopsy examinations and related clinical files of mine workers in the South African mining, quarrying and foundry industries and excluded other industries where asbestos exposure might have occurred, such as construction, as it is embedded in the ODMW Act. In addition, the ODMW Act specifies that an autopsy should be performed for every mine worker, regardless of the cause of death; provided that the next of kin agrees (10,56). This could be

the reason why, in this data set, there were more cases of Black people, as there was a potential benefit of compensation if any occupational disease was ascertained.

4.1.5 Occupation and mesothelioma

There is a large body of knowledge that shows that people who were exposed to asbestos were mainly exposed occupationally. From the Stats SA data, occupation was missing in the majority of cases with mesothelioma. As a result, it is difficult to ascertain the role of occupational exposures in the cases on mesothelioma reported in this study. Nevertheless, the information on occupation provided by Stats SA would have been captured from the death certificate which records 'usual occupation of the deceased' only and, as such, would not have been useful to include in the regression analysis because of the long latency period of mesothelioma after exposure and the move to other jobs after the closing of asbestos mines in 2002 (7).

Most of the studies done in South Africa, focusing on occupational exposures, are circumscribed to studying exposure in asbestos mining and this is from where the highest number of cases are reported (7).

4.1.6 Location: Spatio-temporal analysis by province

Most cases reported in this study were from Gauteng province, from the Stats SA data set, followed by the Northern Cape. The NCR also showed a higher number of cases reported from Gauteng, whereas the ART/KRT reported more cases from the Northern Cape Province. Up to 81% of cases of mesothelioma were reported in the Northern Cape province in previous studies (36), most probably due to the fact that the majority of the asbestos mines in South Africa operated along the asbestos belt in the Northern Cape. The observation of a large number of cases in Gauteng could be associated with the fact that, after the capitulation of the asbestos industry to new safety regulations, and closure of all asbestos mines by 2002, asbestos mine workers migrated to work in other active mining provinces, such as Gauteng and the Free State province (7).

In addition, the diagnosis of mesothelioma is largely done post-mortem, and the main centres equipped with oncology units with the capacity to diagnose mesothelioma are in Gauteng (10). It is important to mention that province of reporting does not necessarily correspond with province where exposure occurred. This is especially important for the Northern Cape

which is the most sparsely populated province in South Africa. People generally migrate from small towns (such as found in the Northern Cape) to the large cities, so the finding is not surprising (57). It is also important to mention that despite the fact that the highest number of cases was found in Gauteng, the Northern Cape had the highest ASMR (Fig 3.5) because of the differences in the population denominators of the provinces, Gauteng having a much larger population compared to the Northern Cape.

In his book published in the early 1980s, Myers described the asbestos storage and transportation processes on the railways as well as in the docks in Cape Town, which could be the reason why so many shipyard, dock, and transport workers could have been exposed and subsequently developed mesothelioma, explaining the high rates in the Western Cape (58).

4.1.7 Mesothelioma Average Annual Percent Change

It is assumed that, due to the higher exposure to asbestos in South Africa in the late 1970's and 1980's, the frequency of mesothelioma is still to peak by 2020 (12), but the analysis of these data showed that there has been a significant decrease of 1.65 % in the trends of mesothelioma deaths during the 11-year study period. This suggests that either a plateau level has been reached in the occurrence of mesothelioma or there is an increase in the underreporting of mesothelioma at the national level. Further investigations will be needed until 2020 to describe the change in mesothelioma trends and draw appropriate conclusions, following the findings of the current study.

4.1.8 Risk factors for mesothelioma

The third objective of this study was to identify factors associated with the trends in mesothelioma mortality in the South African data from 2003 to 2013, using data from Stats SA. Two regression models were fitted to analyse the potential risk factors of mesothelioma mortality with the following independent variables: age, sex and province of death (in the first model), and age, sex and population group (in the second model). This regression analysis was done using the Stats SA data only because they are more representative of the entire country and had more information than the other data sets.

The association between age group and mesothelioma showed a significant difference in the rate of mesothelioma by age group and supports what the current literature shows: that the mortality rate of mesothelioma increases by age. Most of the previous studies showed that the majority of cases of mesothelioma are observed above the age of 70 (59). However, mesothelioma cases in South Africa occur at a unique average of 60 years, possibly due to other competing co-morbidities such as HIV/AIDS and tuberculosis (60). It was found in this study that the MRR of mesothelioma increased exponentially with increasing age.

There was also a significant difference in the risk of mesothelioma between males and females, confirming what has been found in previous studies. The traditional roles of males in the mines, and continued occupational exposure in predominantly male-dominated jobs with more exposure to asbestos, are cited by various authors as probable causes for this observed difference (34,61). However, in the current study, the mortality rate in males was 1.3 times higher than that of females. Contrary to this, previous studies found a male incident risk approximately 5 times greater than that of females (11,28). This suggests that there is underreporting of deaths from mesothelioma among males in South Africa, probably because of other competing causes of death as mentioned previously.

A significant difference in mesothelioma mortality rate by population group was observed, with Indians/Asians having the highest rate when compared Blacks (Ratio: 18/1). This can be explained by the relative population proportions (Indians comprise a very small proportion of the South African population), although there was a huge arithmetic difference in the number of white people (who also comprise a small proportion) with mesothelioma compared to the other races.

In addition, it has been argued that, due to cultural precepts, some black South Africans might have refused to consent to medical autopsies that would have determined the cause of death, to be performed on their deceased relations (56). This supports the hypothesis that there might be underreporting of mesothelioma in the black South African population. There was a statistically significant relationship between province of death and mesothelioma and as shown in other studies: the Northern Cape is a hotspot for asbestos exposure and mesothelioma.

There were about five times more deaths from mesothelioma in the Northern Cape than in the Western Cape, which confirms previous reports that the Northern Cape is a hotspot regarding asbestos exposure and mesothelioma occurrence because of the intense mining activities in the Northern Cape province (62). Surprisingly, there was a significantly lower mesothelioma mortality rate in Gauteng compared to the Northern Cape although, in this study, the absolute number of mesothelioma deaths were found to be high in Gauteng province, and which could be explained by the differences in the population sizes of each province: The Northern Cape having a 10 to 11 times smaller population than Gauteng (Stats SA mid-year provincial populations estimates).

4.2 Strength and limitations of the study

4.2.1 Strengths of the study

The data used in this analysis were from multiple sources which minimised the chances of selection bias. This use of the available sources of data that can provide information on mesothelioma allowed us to provide a more comprehensive view on the extent of mesothelioma in South Africa. In addition, the use of multiple sources allowed for a comparison of the quality of data and the trends in these sources to ascertain and validate the findings with regard to demographic characteristics. Since the data used in this study were routinely collected, standardised, and have the benefit of authenticated case diagnosis, the risk of information bias may be reduced. This was a secondary data analysis that used readily available data on mesothelioma which could be considered representative of each province and the South African population in general.

4.2.2 Limitations

This was a secondary data analysis and, as such, was restricted in terms of the number of factors that could be studied. Any misclassification in the primary data cannot be corrected during secondary data analysis, as selection and systematic bias has already occurred.

In the past, there was a tendency for institutionalised reporting bias on mesothelioma in South Africa to conceal evidence about the toxicity of asbestos by withholding incriminating results from public scrutiny, with the objective of sustaining South African asbestos industry (63). Nevertheless, the ascertainment of mesothelioma is not easy in developing countries as histopathological examinations are not readily available in all provinces of South Africa, and

diagnostic methods such as X-rays are not specific enough to differentiate tumors such as mesothelioma. All the Stats SA data on mesothelioma are based on information found on death certificates, which poses a problem of diagnosis reliability. Concerns about the accuracy of diagnoses on the death certificates has been reported in many countries (64) and, unfortunately, the concordance of cancer diagnosis between the data from Stats SA data and the NCR data could not be evaluated in this study to estimate the extent of under-reporting of mesothelioma in the country.

Stats SA and NCR contain data of national coverage and as such, include all types of mesothelioma due to environmental and occupational asbestos exposure in the entire country. The ARTmis and PATHAUT databases are largely mining-related data. The ARTmis database covers a limited part of the country, while the PATHAUT data are biased towards white miners and younger black miners (pre-retirement) nation. They depend on the results of autopsies performed on deceased miners; cases that do not come to autopsy are missed and therefore contribute to mesothelioma underreporting in the country. In addition, given the short survival time of mesothelioma after diagnosis, there is a greater risk of underreporting cases especially in the case of Stats SA data (65,66).

The administrative databases used for this study were created for either financial compensation (PATHAUT, ART/KRT) or administrative management (Stats SA, NCR) purposes and not for research purpose. As such, they are characterised by lack of data quality control, and missing and incomplete records (67).

The Stats SA data are not available at an individual level, in respect with the Statistics Act legislation related to confidentiality (Section 8 of the Statistics Act, South Africa), which prevents record linkage that would have been useful for the study. The occupation and sub-occupation variables in the dataset did not provide adequate information on actual or potential asbestos exposure which is a crucial factor for mesothelioma development.
Province of death or diagnosis is an inaccurate proxy for place of exposure. People move from one place to another and the place of death or diagnosis might be far from where exposure to asbestos occurred. This shows the existing challenges in the availability and quality of public health services in the country.

The NCR data were only available up to the year 2010 at the time of data collation. These data are obtained from public and private laboratories and, as such, clinical misdiagnosis and missed cases cannot be accounted for. The passive nature of cancer surveillance can be affected by delays in the reporting of cancer cases and, even if mandatory, some laboratories submit only summary reports, or submit reports sporadically (14). All cases of mesothelioma, even if diagnosed clinically, might have not been histologically diagnosed at pathology laboratories, resulting in under-reporting.

The PATHAUT data set provides data for primarily occupational asbestos exposure and is limited to workers from the mining and foundry industries. Other industries that used asbestos are not represented, e.g. construction, demolition, and insulation companies.
The Stats SA, NCR, and PATHAUT databases use a passive reporting system to collect data based on death certificates or pathology reports while the ARTmis database uses both active and passive approaches. Active surveillance system is expensive to maintain and might not currently be feasible for the NCR and Stats SA.

The ART/KRT data provide information related to only those claimants who worked or lived in the vicinity of specific asbestos mines, as specified in the conditions of the Trusts (68). Hence, there are geographic and time-bound limitations with respect to coverage of mesothelioma and asbestos-related diseases. In addition, race or ethnic group of the claimants is not recorded in the ARTmis data set, preventing the comparison of disease by race.

CHAPTER 5 : RECOMMENDATIONS AND CONCLUSION

5.1 Recommendations

One of the objectives of this study was to provide estimates of the burden of mesothelioma in South Africa by evaluating information from different data sources, and calculating the mesothelioma mortality and incidence rates. Establishing a collaborative repository for collecting and tracking data on mesothelioma mortality is one of the main recommendations that come from this study because of the necessity for data linkage between different data sets to generate more reliable annual estimates of mesothelioma burden in the country. Indeed, if Stats SA, the NCR and the ART/KRT used a standardized identification system to allow for cases to be linked across their databases, it would assist in a more valid assessment of the impact that the ban on asbestos has had (and will continue to have) on the incidence of mesothelioma, as the number, and hence rates, of cases could be more accurately estimated.

Data collected for individuals by the different agencies responsible for data collection, including Stats SA and the NCR, failed to include some critical information on the demographic, occupational, and lifestyle-related characteristics such as smoking and alcohol usage. There is need to improve and standardize the data collection tools to ensure that all mesothelioma cases are recorded and have complete data for effective comparison of the different data sets.

There is a need for active contact tracing and further studies to ascertain the extent to which migration could be contributing to lower estimates of mesothelioma amongst all races.

For future research, there is need to use a standardised method to collect data related to other important factors that are imperative in helping to identify individuals at risk of developing mesothelioma. This will assist in the design of interventions to increase the protection of people from the risk of mesothelioma, particularly given its poor prognosis and short survival period after diagnosis.

There is also a need for a renewed action by government to support the existing policy (Regulation: OHS - Asbestos Regulations 2001) in reducing environmental exposure in the country from asbestos mine dumps and demolished buildings that contain asbestos, to prevent

the occurrence of mesothelioma cases in the future. Awareness should be raised on the measures that should be taken if any building material (roof tiles, for example) is suspected to be containing asbestos. There is a need for the suspected material to be tested by specialised services of Environmental Health and Safety as offered by the NIOH. In addition, air monitoring should also be conducted in communities surrounding old asbestos mines or asbestos dumps; if the exposure limits are exceeded, measures should be put in place to reduce the levels, such as adequately and appropriately covering exposed dumps.

5.2 Conclusion

The patterns of mesothelioma observed in this study suggest a decreasing trend in mesothelioma incidence and mortality in South Africa, contrary to previous predictions anticipating an increasing trend until 2022. It can therefore be assumed that the peak of mesothelioma has already occurred. Mesothelioma in South Africa is certainly underreported. There are several different institutions that are collating data on mesothelioma but their purposes for data collection are different and there is no established collaborative effort to standardize and improve the tracking of the disease. Despite a decreasing trend in mesothelioma that was identified from analysing the available data, the full extent of the burden of mesothelioma remains unknown. Asbestos contamination in the environment will continue to cause mesothelioma cases, despite the ban on the use and mining of asbestos. Surveillance for mesothelioma in South Africa is mostly passive, and relies on identifying the disease when the adverse outcomes have already occurred. Public awareness should be raised at both occupational health practitioner and community levels to identify people who are at risk of developing mesothelioma or asbestos-related diseases because of past or current exposure to asbestos dust. In addition, record linkage should be used to assess the accuracy of the mesothelioma official statistics.

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APPENDICES

Appendix 1: 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, Dr Kasongo Michel Muteba (Student number: 85414), am a student registered for the degree of Master of Science in Epidemiology in the academic year 2015/2016.

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: 31 August 2017

26/04/2015
1

Appendix 2: List of variables in each data set

#	Stats SA	NCR	PATHAUT/NIOH	ART/KRT
1	Serial number	Registration number	Pathology number	File number
2	Type of death	Age	Received date	Registration date
3	Year of death	Date of Birth	Examination date	Gender
4	Month of death	Sex	Report date	Age at registration
5	Day of death	Population group	Gender	Date of birth
6	Year of birth	Date of diagnosis	Date of birth	Date of death
7	Month of birth	Centre code	Date of death	died
8	Day of birth	Centre name	Age	Place of death
9	Age in completed years	Mesothelioma description	Pathology code	Region
10	Year of death registration	Province	Report status	Claim reference number
11	Month of death registration	Hospital	Cause of death1 on death certificate	Claimant type
12	Day of death registration		Cause of death2 on death certificate	Claim area
13	Sex of deceased		Cause of death3 on death certificate	Claim handler
14	Marital status of deceased		code description	Claim status
15	Relationship of informant to deceased		Cause of death 1 Pathologist	Status date
16	Next of kin a smoker		Cause of death 2 Pathologist	Office
17	Education of deceased		Cause of death 3 Pathologist	Diagnosis type
18	Occupation of deceased		Pathology description	Year of first exposure
19	Groups of occupation of deceased		Population group	Medical panel date
20	Industry of deceased		Year employment start	Chest X-ray date
21	Smoking status of deceased		Year employment end	Doctor
22	Citizenship of deceased		Last mine	Other abnormalities

23	Province of birth of the deceased	Regional glands TB	Other diseases
24	Province of death occurrence	Miliary TB	Number of months of employment
25	Province of usual residence of the deceased	Lung TB	Number of years of employment
26	Country of usual residence of deceased	Pleural mesothelioma	Age in years
27	Ascertainment of the cause of death	epithelial mesothelioma	Height in meter
28	Death Inst/Place of death	sarcomatous mesothelioma	Weight in Kg
29	Immediate cause of death	opinion silicosis	Smoking status
30	Immediate cause of death	opinion asbestos related disease	Diagnosis type
31	Injury codes for the immediate cause of death	opinion coal worker's pneumoconiosis	Pulmonary TB
32	Second condition leading to death	opinion mixed dust fibrosis	
33	Injury codes for the second condition leading to death		
34	Third condition leading to death		
35	Injury codes for the third condition leading to death		
36	Fourth condition leading to death		
37	Injury codes for the fourth condition leading to death		
38	Other conditions leading to death		
39	Injury codes for other conditions leading to death		
40	First cause provided on part 2 of the death notification form		
41	Injury codes for first cause		

	on part 2
42	Second cause provided on part 2 of the death notification form
	Injury codes for second
43	cause on part 2
44	Underlying cause of death
	Broad groups of the underlying causes of
45	death
46	Main groups of the underlying causes of death
	Natural/non-natural underlying causes of
47	death
48	underlying causes of death

Appendix 3: World standard population (2000)

Age Group	WHO World Standard (%)	Recalculation to add to 1,000,000	Rounded to Integers	Standard For SEER*Stat
0-4	8.86	88569.00085	88,569	88,569
5-9	8.69	86869.59564	86,870	86,870
10-14	8.6	85969.91053	85,970	85,970
15-19	8.47	84670.36537	84,670	84,670
20-24	8.22	82171.24007	82,171	82,171
25-29	7.93	79272.25471	79,272	79,272
30-34	7.61	76073.37432	76,073	76,073
35-39	7.15	71474.98376	71,475	71,475
40-44	6.59	65876.94307	65,877	65,877
45-49	6.04	60378.8674	60,379	60,379
50-54	5.37	53681.21158	53,681	53,681
55-59	4.55	45484.08057	45,484	45,484
60-64	3.72	37186.98456	37,187	37,187
65-69	2.96	29589.64362	29,590	29,590
70-74	2.21	22092.26771	22,092	22,092
75-79	1.52	15194.68186	15,195	15,195
80-84	0.91	9096.816114	9,097	9,097
85-89	0.44	4398.460539	4,398	4,398
90-94	**0.15**	**1499.475184**	**1,499**	**1,500***
95-99	0.04	399.860049	400	400
100+	0.005	49.98250612	50	50
Total	100.035	1000000	999,999	1,000,000

Appendix 4: Average annual mesothelioma death counts by province of death, South Africa (Stats SA 2003-2013)

Province of Death	mean	variance	n
Western Cape	195.1	258.1	402
Eastern Cape	195.0	226.0	104
Northen Cape	195.1	261.7	442
Free State	193.7	273.3	118
KwaZulu-Natal	197.0	241.5	150
North West	197.3	216.2	151
Gauteng	194.2	248.9	635
Mpumalanga	195.6	249.2	65
Limpopo	197.7	255.1	65
Total	195.1	251.1	2132

Appendix 5: Cross Table of mesothelioma deaths by province of death and province of residence (Stats SA)

	Province of residence										
Province of death	**Western Cape**	**Eastern Cape**	**Northern Cape**	**Free State**	**KwaZulu-Natal**	**North West**	**Gauteng**	**Mpumalanga**	**Limpopo**	**Unspecified**	**Total**
Western Cape	353	1	0	0	0	1	4	0	0	43	402
Eastern Cape	2	85	0	0	1	0	0	1	0	15	104
Northern Cape	4	2	395	0	0	5	0	0	2	34	442
Free State	0	1	7	100	0	0	3	0	0	7	118
KwaZulu-Natal	6	1	0	1	108	0	1	0	2	31	150
North West	3	1	9	5	0	103	3	0	0	27	151
Gauteng	1	3	2	15	3	9	519	7	4	72	635
Mpumalanga	0	2	0	0	0	0	2	51	1	9	65
Limpopo	0	0	2	0	1	0	1	0	53	8	65
Total	**369**	**96**	**415**	**121**	**113**	**118**	**533**	**59**	**62**	**246**	**2 132**

Appendix 6: Wits HREC clearance certificate and data user agreement letters

R14/49 Dr Kasongo Michel Muteba and Prof Benn Sartorius

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M151167

NAME: (Principal Investigator)	Dr Kasongo Michel Muteba and Prof Benn Sartorius
DEPARTMENT:	Public Health University of the Witwatersrand
PROJECT TITLE:	Mesothelioma Incidence and Mortality in South Africa From 2003 to 2013
DATE CONSIDERED:	27/11/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Gill Nelson
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	11/03/2016

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 Secretary in Room 10004, 10th floor, Senate House, University.

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

Principal Investigator Signature Date 15/03/2016

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Statistics South Africa

The South Africa I know, the home I understand

Enquiries: Kefiloe Masiteng
Reference: Unit records of data
Telephone: 012 310 4663
Email: KefiloeM@statssa.gov.za

STATISTICS SOUTH AFRICA
DATA USER'S AGREEMENT: UNIT RECORDS, MORTALITY AND CAUSES OF DEATH DATA

Statistics South Africa will make available unit record data compiled from death notification forms for the purpose of undertaking research on mesothelioma incidence and mortality in South Africa (2003–2013). The additional variables requested are population group and district municipality of death occurrence.

The Data User must ensure that there is no misuse of the Data or breach of confidentiality and must agree to the following conditions:

1. The User agrees that he/she will not attempt to use, nor permit other to use the Data to establish the identify of any person included in any set.
2. The User agrees that he/she will keep the Data in a secure environment.
3. The Data may be used only by the User and his/her named collaborative research team and may not be shared with other Users. The following Users will be working on the Data:
    i. Dr Michel Muteba
4. The User agrees that any of the Data, or reliance by the User on any of the Data, is at the User's own risk, and that Statistics South Africa shall not be liable for any loss or damage howsoever arising as a result of such use.
5. The use of these Data in research communication, scholarly papers, journals and the like is encouraged, but the authors of these communications and documents agree to acknowledge/cite Statistics South Africa as the source of the Data, making it clear that the analysis and interpretation have been undertaken by the User. The User also agrees to submit to Statistics South Africa a copy of any research publication derived from these Data, for their information.
6. Non-adherence to the above conditions will result in:
    i. Render the User liable for the amount of ZAR 500 000 (Five hundred thousand Rands)
    ii. Statistics South Africa refusing to make available any datasets to the User in future.

7. Signatures of Users:

i. Name: Dr Michel Muteba
Organisation: Wits School of Public Health
Signature:
Signed on: 27-January-2016
Signed at: Johannesburg

Kefiloe Masiteng

DDG: Population and Social Statistics – Statistics South Africa
Date: 29/01/16

NATIONAL HEALTH
LABORATORY SERVICE
National Cancer Registry

National Cancer Registry
De Korte Street, Braamfontein, Johannesburg, 2000
Tel: +27 (0)11 489 9026 Fax: +27 (0)11 489 9152
Reference:

Date: 01/12/2015

Dear: Sir/Madam

Re: Data request to the National Cancer Registry for Protocol Ref: M151167

The National Cancer Registry has reviewed the protocol "Mesothelioma incidence and mortality in South Africa from 2003 to 2013" and has agreed to provide non-identifiable data to Dr Michel Muteba for this study on condition that ethics approval has been obtained from the appropriate Human Research Ethics Committee.

Yours sincerely

Dr E Singh
Head of Department (Acting)
National Cancer Registry
National Health Laboratory Service

Dr Jim teWaterNaude
MBChB, MPhil MCH, FCPHM
Public Health Medicine Specialist
PR No. 014 000 1531549 & MP 0301515

104 Library Square
Wilderness Road
7708 CLAREMONT
Weekdays 08:00-16:00

dr@drjim.co.za
Tel 021 671 3084
Fax 0866 104 012
Cell 082 417 2228

8 March 2016

The Chairperson
University of the Witwatersrand Human Ethics Committee.

Dear Chairperson

Study title: Mesothelioma incidence and mortality in South Africa from 2003.
University of the Witwatersrand Human Ethics Committee Protocol Reference No. M151167
Principal Investigator: Dr Kasongo Michel Muteba

As the custodian of the medical information in the ARTMIS database, and on behalf of the Asbestos and Kgalagadi Relief Trusts (ART and KRT), I hereby grant Dr Kasongo Michel Muteba, a student under the tutelage of Prof Gillian Nelson, access to the medical data in the ARTMIS database of the ART and KRT for the purposes of carrying out his study titled Mesothelioma incidence and mortality in South Africa from 2003, which carries the University of the Witwatersrand Human Ethics Committee Protocol Reference No. M151167.

This is done subject to the highest ethical standards being maintained throughout the conduct of the envisaged research. This issue was discussed, agreed to and minuted at the joint meeting of the ART and KRT on 16 February 2016.

Sincerely,

JM teWaterNaude

Dr James Mark te Water Naude

www.drjim.co.za

NATIONAL INSTITUTE FOR OCCUPATIONAL HEALTH
Division of the National Heralth Laboratory Service

25 Hospital Street, Constitution Hill ● PO Box 4788 Johannesburg 2000 South Africa ● Tel: 27 11 712 6519 ●Fax: 27 11 712 6450

DATA USER'S AGREEMENT
NATIONAL INSTITUTE FOR OCCUPATIONAL HEALTH

I, (f*ull name*) **Dr Kasongo Michel MUTEBA**,
agree to use the data set of the National Institute for Occupational Health (NIOH) exclusively in relation to an analysis of (*project title*) **Mesothelioma Incidence and Mortality in South Africa from 2003 to 2013**,as discussed with, and in collaboration with, the NIOH.

The results will be used for the purpose of (*project; degree, study or publication – state which)* ***MSc degree in Epidemiology and Biostatistics.***

Attached is a protocol outlining the proposed study.

The user agrees that he/she will

1. not share any part of the data set with other parties;

2. keep the data in a secure environment;

3. not to attempt to use, nor permit other use of the data to establish the identity of any person included in the dataset;

4. not use the data in any publications or presentations unless previously discussed and approved by the NIOH and collaborators. All presentations and publications arising from this work will have the following NIOH staff and collaborators as co-authors, dependent on their contributions:
Naseema Vorajee (Pathology Division, NIOH)

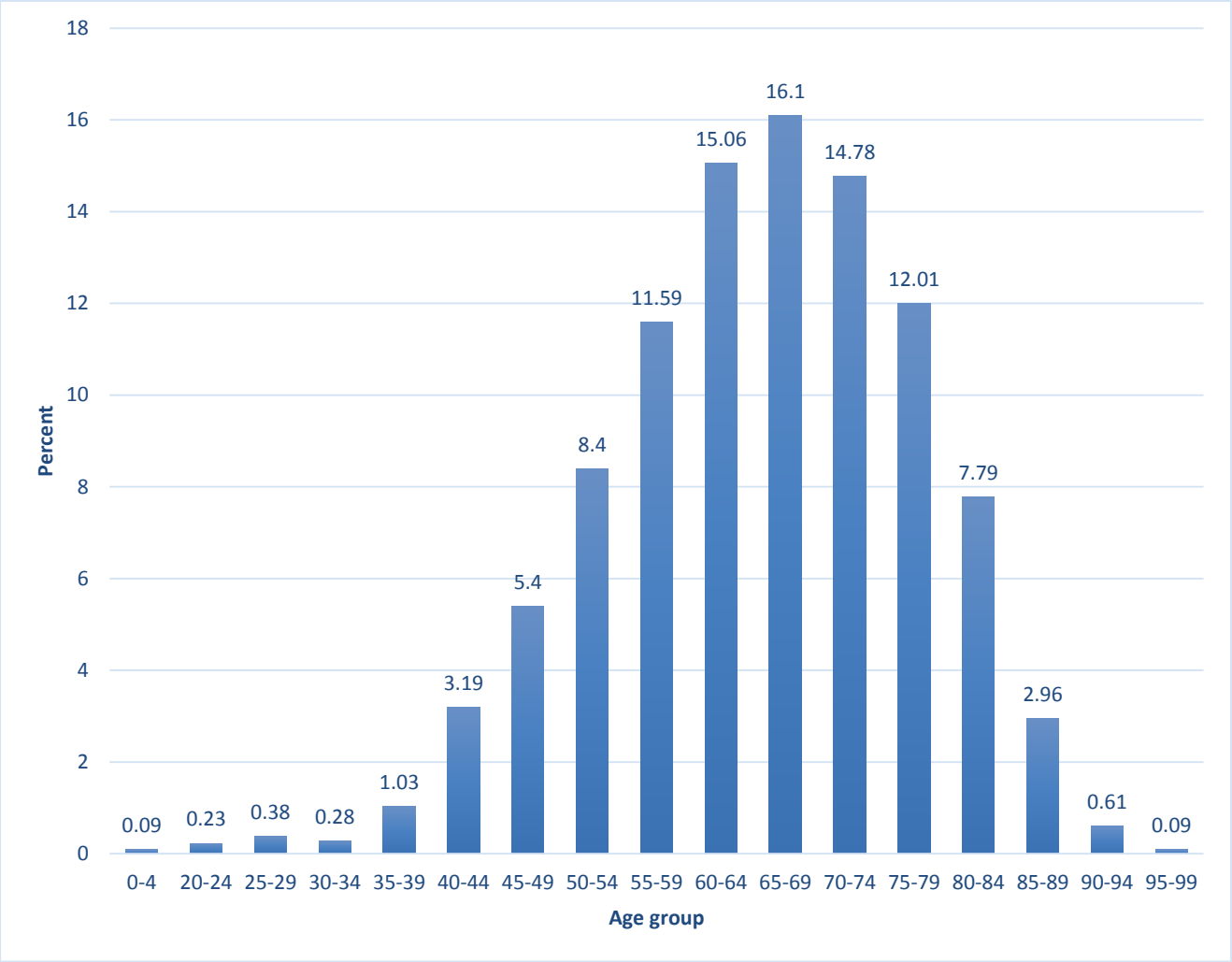
Publication is expected within 12 months of receiving the requested data. The NIOH reserves the right to reassign leadership of the analysis if unjustified delays occur. Project completion is expected by (d*ate*) **December 31, 2016.**

Dr KM MUTEBA	
Name	Signature
Wits School of Public Health	18/01/2016
Affiliation	Date
Prof Gill Nelson	18/01/2016
Name and signature of Supervisor (if applicable)	Date

Appendix 7: Age-Standardized Incidence rate per 1000 000 World standard population of mesothelioma, South Africa(NCR 2003-2010)

Age group	2003	2004	2005	2006	2007	2008	2009	2010
0-4	0	0	0	0	0	0	0	0
5-9	0	0	0	0	0	0	0	0
10-14	0	0	0	0	0	0	0	0
15-19	0	0	0	0	0	0	0	0
20-24	0	0	0.002	0	0.002	0	0	0
25-29	0	0.002	0.002	0	0.002	0	0.002	0
30-34	0	0.002	0.002	0.002	0.000	0	0	0
35-39	0.011	0.010	0.008	0.013	0.005	0.005	0.011	0.004
40-44	0.024	0.031	0.008	0.009	0.022	0.003	0.011	0.010
45-49	0.035	0.033	0.025	0.035	0.022	0.019	0.032	0.019
50-54	0.100	0.040	0.043	0.041	0.037	0.069	0.045	0.045
55-59	0.091	0.086	0.064	0.081	0.049	0.081	0.050	0.055
60-64	0.116	0.053	0.069	0.070	0.071	0.077	0.054	0.062
65-69	0.119	0.139	0.071	0.064	0.077	0.080	0.055	0.075
70-74	0.051	0.099	0.108	0.046	0.063	0.055	0.062	0.041
75-79	0.073	0.039	0.066	0.045	0.040	0.086	0.046	0.048
80+	-	0.095	0.042	0.036	0.030	0.039	0.048	0.038
Total	0.619	0.629	0.508	0.442	0.419	0.514	0.417	0.399

Appendix 8: Frequency distribution of Mesothelioma deaths by age group (Stats SA 2003- 2013)

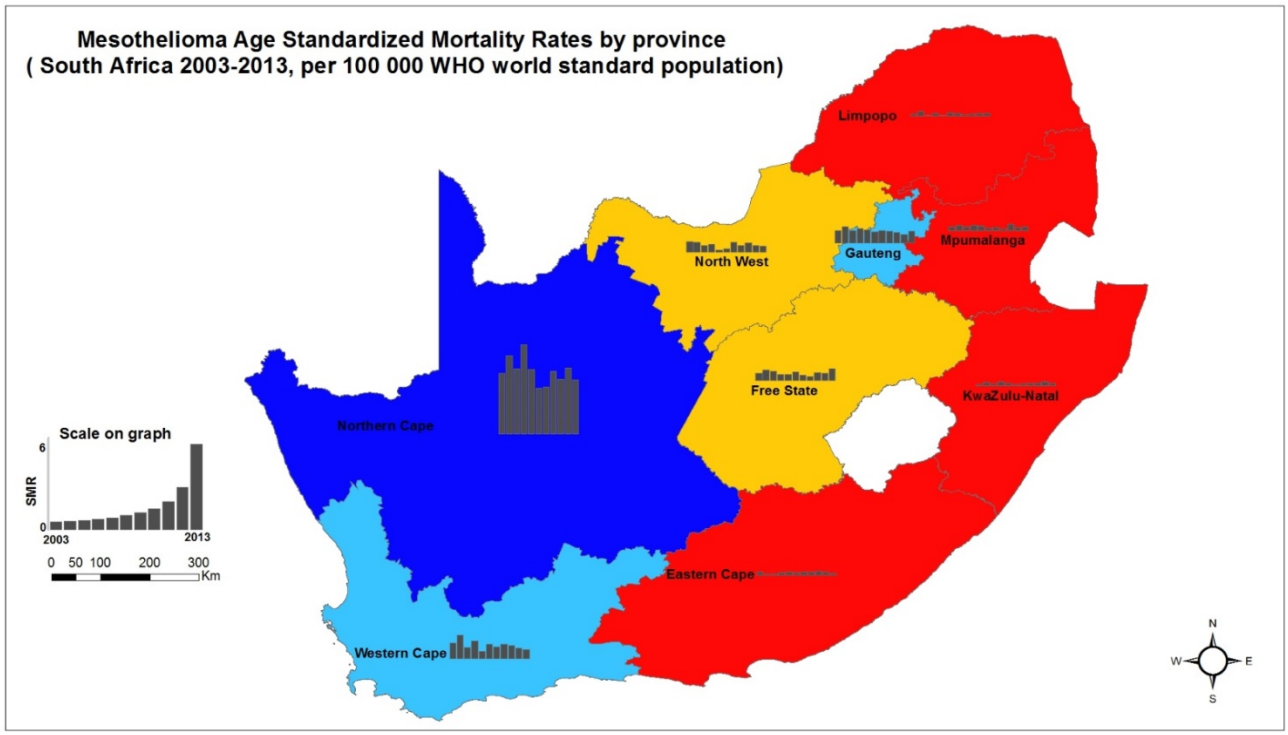


Appendix 9: Age-Standardized Mortality rate per 1000 000 World standard population of Mesothelioma by age group (Stats SA 2003 =-2013)

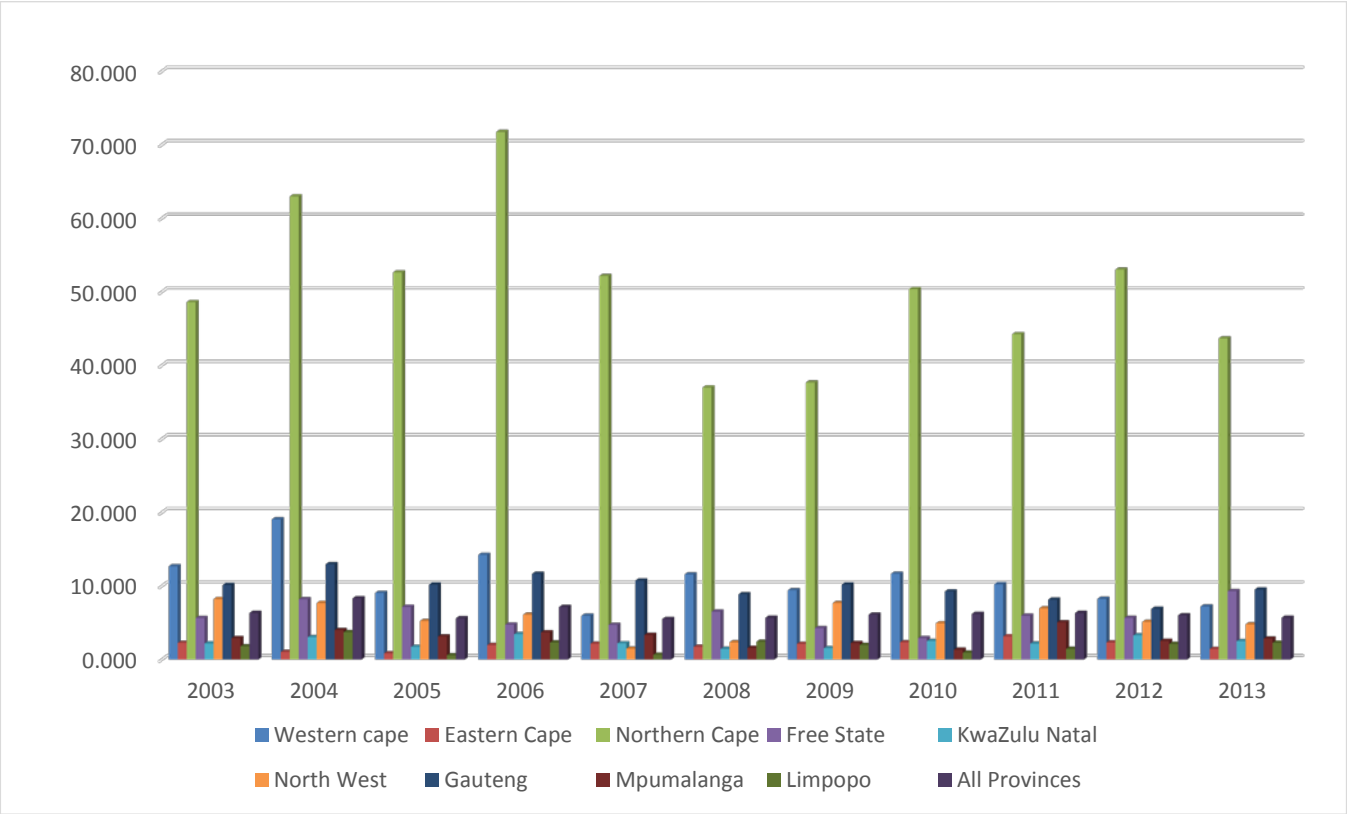
Age group	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
0-4	0	0	0	0.002	0	0	0	0	0.002	0	0
5-9	0	0	0	0.002	0	0	0	0	0.002	0	0
10-14	0	0	0	0.002	0	0	0	0	0.002	0	0
15-19	0	0	0	0.002	0	0	0	0	0.002	0	0
20-24	0	0	0.004	0.004	0	0	0	0	0	0.002	0
25-29	0.002	0	0.002	0.002	0.004	0	0.002	0	0	0.002	0.002
30-34	0.004	0	0.002	0.002	0	0	0	0	0.002	0.002	0
35-39	0.009	0.003	0.010	0.015	0.007	0	0.002	0.004	0.002	0	0
40-44	0.017	0.016	0.029	0.036	0.022	0.011	0.011	0.013	0.010	0.009	0.006
45-49	0.032	0.035	0.022	0.046	0.019	0.027	0.035	0.030	0.022	0.017	0.021
50-54	0.072	0.064	0.031	0.053	0.037	0.044	0.047	0.053	0.037	0.035	0.026
55-59	0.076	0.073	0.090	0.069	0.055	0.058	0.066	0.066	0.060	0.053	0.061
60-64	0.102	0.096	0.090	0.091	0.085	0.080	0.086	0.082	0.094	0.063	0.074
65-69	0.086	0.189	0.071	0.106	0.077	0.070	0.086	0.096	0.105	0.110	0.081
70-74	0.067	0.133	0.081	0.105	0.120	0.069	0.095	0.099	0.087	0.095	0.085
75-79	0.164*	0.117	0.050	0.082	0.047	0.114	0.082	0.083	0.096	0.093	0.082
80+	*	0.106	0.079	0.094	0.077	0.092	0.097	0.093	0.112	0.120	0.130
Total	**0.632**	**0.832**	**0.560**	**0.712**	**0.550**	**0.566**	**0.609**	**0.619**	**0.632**	**0.601**	**0.567**

For year 2003, the ASMR of 0.164/100 000 population of for age group of 75 and above

Appendix 10:Graphical mapping summary of Age-Standardized Mortality rate per 100 000 World standard population (WHO 2000) of Mesothelioma, South Africa, 2003-2013, by province



Appendix 11: Frequency distribution of mesothelioma by province, South Africa (Stats SA 2003-2013)



Appendix 12:Unadjusted negative binomial regression analysis of factors associated with mesothelioma deaths

		MRR	P>z	95% CI	
Age group	0-9	1.000	Base		
	20-29	0.935	0.260	0.832	1.051
	30-39	0.966	0.536	0.866	1.078
	40-49	0.957	0.407	0.862	1.062
	50-59	0.946	0.299	0.853	1.050
	60-69	0.952	0.350	0.857	1.056
	70-79	0.948	0.313	0.854	1.052
	80-89	0.943	0.274	0.849	1.047
	90-99	0.961	0.480	0.860	1.073
Sex	Male	1.000	Base		
	Female	1.000	0.964	0.991	1.009
Population Group	Black	1.000	Base		
	White	0.998	0.742	0.987	1.010
	Indian/Asian	0.973	0.168	0.937	1.011
	Coloured	0.995	0.557	0.980	1.011
	unspecified	0.996	0.575	0.984	1.009
Marital status	Never Married	1.000	Base		
	Married	0.991	0.120	0.980	1.002
	Widowed	0.997	0.707	0.983	1.012
	Divorced	0.997	0.701	0.981	1.013
	unspecified	0.995	0.484	0.981	1.009
Smoking	No	1.000	Base		
	Yes	0.997	0.644	0.986	1.009
	unspecified	1.003	0.514	0.993	1.013
Province of death	Western Cape	1.000	Base		
	Eastern Cape	1.001	0.957	0.967	1.036
	Northen Cape	1.000	0.977	0.969	1.033
	Free State	0.978	0.272	0.939	1.018
	KwaZulu-Natal	0.995	0.753	0.962	1.028
	North West	1.016	0.314	0.985	1.048
	Gauteng	0.994	0.645	0.967	1.021

	Mpumalanga	0.977	0.289	0.937	1.020
	Limpopo	1.000	0.997	0.961	1.040
Province of residence	Western Cape	1.000	Base		
	Eastern Cape	0.991	0.602	0.956	1.026
	Northern Cape	0.998	0.903	0.966	1.031
	Free State	1.015	0.480	0.974	1.057
	KwaZulu-Natal	1.014	0.448	0.978	1.052
	North West	0.986	0.390	0.954	1.018
	Gauteng	1.001	0.920	0.974	1.030
	Mpumalanga	1.025	0.254	0.982	1.070
	Limpopo	1.009	0.669	0.970	1.049
	unspecified	1.019	0.125	0.995	1.044
Education	None	1.000	Base		
	grade R to 6	1.003	0.834	0.977	1.029
	grade 7 -11	0.985	0.210	0.962	1.009
	Matric	0.981	0.133	0.957	1.006
	University/Tech	0.985	0.282	0.959	1.012
	unspecified	0.991	0.422	0.969	1.013
Institution of death	Hospital	1.000	Base		
	Emergency room/outpatient	0.985	0.402	0.950	1.021
	Dead on arrival	0.994	0.568	0.975	1.014
	Nursing home	0.995	0.572	0.979	1.012
	Home	1.005	0.303	0.996	1.014
	Other	1.000	0.995	0.977	1.023
	Unknown	0.978	0.451	0.924	1.036
	Unspecified	1.003	0.633	0.991	1.015
Sub-occupation	Occupation unspecified	1.000			
	Not economically active	1.000	0.924	0.993	1.008
	senior officials, administrative, and commercial managers	1.034	0.149	0.988	1.082
	market oriented, food processing, wood, agriculture, hunting, forestry and fisheries.	1.002	0.905	0.966	1.040
	hospitality, retail, general and other services	1.008	0.722	0.963	1.056
	teaching, Science and engineering professionals.	0.975	0.225	0.936	1.016
	life &health science, and health professionals	0.971	0.175	0.930	1.013
	Protective service workers and armed force occupation	0.966	0.339	0.900	1.037

	business and administration, information and communication technology professionals	0.958	0.046	0.919	0.999
	legal, social and cultural and related associate professionals	0.987	0.594	0.942	1.035
	mining, building and related workers, transport, manufacturing	1.008	0.706	0.966	1.053
	metal, machinery, stationary plant, electrical and electronic, and related trade workers	1.009	0.706	0.965	1.054
	handicraft and printing workers, assemblers	1.042	0.073	0.996	1.091
	street and related sales and service workers, refuse workers and other elementary workers	0.972	0.241	0.927	1.019
	drivers and mobile plant operators	1.011	0.670	0.961	1.064
Occupation group	Armed forces/occupations unspecified and not elsewhere classified/not economically acti..	1.000			
	Legislators/senior officials/managers	0.987	0.523	0.948	1.027
	Professionals	1.036	0.092	0.994	1.080
	Technicians and associate professionals	1.031	0.195	0.984	1.081
	Clerks	0.989	0.700	0.933	1.048
	Service workers_shop and market sales workers	1.015	0.650	0.951	1.084
	Skilled agricultural and fishery workers	1.012	0.655	0.960	1.067
	Craft and related trade workers	1.000	0.986	0.956	1.047
	Plant and machine operators and assemblers	0.973	0.248	0.928	1.019
	Elementary occupations	1.014	0.551	0.969	1.061
	Unspecified	1.045	0.000	1.030	1.061

Appendix 13:Adjusted negative binomial regression analysis of factors associated with mesothelioma deaths (Model 1)

Negative binomial regression — Number of obs = 2,131
Wald chi2(13) = 65160.98
Dispersion = constant — Prob > chi2 = 0.0000
Log pseudolikelihood = -10985.135 — Pseudo R2 = 0.2891

count_death	IRR	Robust Std. Err.	z	P>|z|	[95% Conf.	Interval]
Age_group						
<20years	1	(base)				
20-39 years	1.413649	.0712442	6.87	0.000	1.280687	1.560414
40-59 years	2.628535	.1089793	23.31	0.000	2.423387	2.851049
60-74 years	8.0931	.3281127	51.58	0.000	7.474898	8.76243
75+ years	33.91264	1.434056	83.33	0.000	31.21527	36.8431
Sex						
Male	1.304885	.0166284	20.88	0.000	1.272698	1.337887
Female	1	(base)				
DeathProv_2011						
Western Cape	1	(base)				
Eastern Cape	.8092121	.0226985	-7.55	0.000	.7659246	.8549461
Northen Cape	4.920991	.0637413	123.02	0.000	4.797633	5.047521
Free State	2.022561	.0392213	36.32	0.000	1.947131	2.100913
KwaZulu-Natal	.6760572	.0117104	-22.60	0.000	.6534905	.6994032
North West	1.565444	.0255035	27.51	0.000	1.516248	1.616237
Gauteng	.5448157	.0072722	-45.50	0.000	.5307473	.5592569
Mpumalanga	1.891379	.0467772	25.77	0.000	1.801884	1.985319
Limpopo	1.2635	.0659279	4.48	0.000	1.140672	1.399555
_cons	.0001206	5.18e-06	-210.24	0.000	.0001109	.0001312
ln(Prov_est~s)	1	(exposure)				
/lndelta	2.049792	.0459154			1.959799	2.139785
delta	7.766286	.3565924			7.097903	8.497608

Appendix 14: Negative binomial regression model fit information for Model 1

```
. fitstat
```

	nbreg
Log-likelihood	
Model	-10985.135
Intercept-only	-15452.665
Chi-square	
Deviance (df=2116)	21970.271
Wald (df=13)	65160.980
p-value	0.000
R2	
McFadden	0.289
McFadden (adjusted)	0.288
Cox-Snell/ML	0.985
Cragg-Uhler/Nagelkerke	0.985
IC	
AIC	22000.271
AIC divided by N	10.324
BIC (df=15)	22085.236

```
Note: Some measures based on pseudolikelihoods.
```

Appendix 15: Adjusted negative binomial regression analysis of factors associated with mesothelioma (Model 2)

```
Negative binomial regression                    Number of obs     =      1,746
                                                Wald chi2(8)      =  83676.76
Dispersion           = constant                 Prob > chi2       =    0.0000
Log pseudolikelihood = -8958.8459               Pseudo R2         =    0.3139
```

count_death	IRR	Robust Std. Err.	z	P>|z|	[95% Conf.	Interval]
Age_group						
<20years	1	(base)				
20-39 years	1.62492	.1093663	7.21	0.000	1.424103	1.854055
40-59 years	3.227956	.1357095	27.87	0.000	2.972634	3.505207
60-74 years	9.247254	.3982205	51.65	0.000	8.498787	10.06164
75+ years	31.97652	1.457112	76.04	0.000	29.24446	34.96383
Sex						
Male	1.307067	.0162833	21.50	0.000	1.275539	1.339375
Female	1	(base)				
PopGroup_new						
Black	1	(base)				
White	3.085161	.0478641	72.62	0.000	2.992761	3.180413
Indian/Asian	18.75556	.7118186	77.24	0.000	17.41105	20.2039
Coloured	7.004299	.1289101	105.76	0.000	6.756143	7.261571
_cons	.0000189	8.06e-07	-254.60	0.000	.0000173	.0000205
ln(Racepop~s)	1	(exposure)				
/lndelta	2.000296	.0437999			1.91445	2.086142
delta	7.391242	.3237356			6.783204	8.053784

Appendix 16: Negative binomial regression model fit information for Model 2

```
. fitstat, diff force
```

	Current	Saved	Difference
Log-likelihood			
Model	-8958.846	-10985.135	2026.290
Intercept-only	-13057.911	-15452.665	2394.754
Chi-square			
D (df=1736/2116/-380)	17917.692	21970.271	-4052.579
Wald (df=8/13/-5)	83676.762	65160.980	18515.782
p-value	0.000	0.000	1.000
R2			
McFadden	0.314	0.289	0.025
McFadden (adjusted)	0.313	0.288	0.025
Cox-Snell/ML	0.991	0.985	0.006
Cragg-Uhler/Nagelkerke	0.991	0.985	0.006
IC			
AIC	17937.692	22000.271	-4062.579
AIC divided by N	10.274	10.324	-0.050
BIC (df=10/15/-5)	17992.343	22085.236	-4092.893
N			
N	1746.000	2131.000	-385.000

```
Note: Some measures based on pseudolikelihoods.

Note: Likelihood-ratio test assumes current model nested in saved model.

Difference of 4092.893 in BIC provides very strong support for current model.
```

The model with population group variable fits the data much better than the model with province of death, seeing that it has smaller Akaike's information criterion (AIC) and the Bayesian information criterion (BIC) values