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TRENDS AND DETERMINANTS OF THE INCIDENCE AND MORTALITY OF CERVICAL CANCER IN SOUTH AFRICA (1994-2012)

Gbenga Olorunfemi

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 the field of Epidemiology and Biostatistics.

Johannesburg, June 2017

DECLARATION

I, Dr Gbenga Olorunfemi declare that this research report is my unaided work. It is being submitted in partial fulfilment for the degree of Master of Science in Epidemiology in the field of Epidemiology and Biostatistics, Faculty of Health Sciences at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Signature of candidate___Gfemi_____

_18 TH_____ day of ___JUNE_____, 2017

In memory of

My father, Ololu Paul Dare Olorunfemi

1945-2006

And

My supervisor, late Dr Danuta Kielkowski, (PHD)

LIST OF CONFERENCE PRESENTATIONS FROM THIS STUDY.

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ABSTRACT

Cervical cancer (CC) is the leading cause of female cancer morbidity and mortality in South Africa, despite the introduction of preventive programs. However, there is a paucity of information on current CC rates and trends in South Africa. This study aimed to evaluate the national trends and determinants of CC over a 19 year period (1994-2012).

We conducted temporal analyses of age-standardised incidence rates (ASIR) from 1994 to 2009 and age-standardised mortality rates (ASMR) from 2004 to 2012 using data from the National Cancer Registry and Statistics South Africa, respectively. We also evaluated a novel surrogate measure (complement of MR: IR ratio) to calculate five-year relative survival rates of CC (2004-2009). Temporal analyses were stratified by the province of residence, histological type, population- and age-groups, while linear regression models were fitted to determine the average annual percent change (AAPC) of the time trends. Spatial distribution was conducted by utilising the GIS coordinates of SA to map the provincial ASMR. Unconditional logistic regression analyses were carried out for three case-control studies using data from the hospital-based Johannesburg Cancer Case-Control Study (JCCCS) (1995-2010), to evaluate the effect of HIV infection; tobacco smoking and alcohol abuse and sexual and reproductive behaviours on the risk CC in Black South Africans. The cases were participants with CC while controls were other female cancer participants that had no known association with CC and its risk factors.

There were 75,099 incident cases and 25,101 mortalities from CC in the periods studied with women below 50 years accounting for 43.1% of the cases and 35.7% deaths. The ASIR was 22.1/100,000 in 1994 and 23.3/100,000 in 2009 and there was an average annual decrease in incidence of 0.9% (AAPC=-0.9%, P-value<0.001). The ASMR decreased slightly from 13.9/100,000 in 2004 to 13.1/100,000 in 2012 (AAPC = -0.6%, P-value < 0.001). Based on current trends, the ASIR and ASMR were predicted to increase to 26.3/100,000 and 14.6/100,000 in 2030, respectively. From 2004 to 2012, five provinces had increased mortality rates (AAPC: 1.2 – 8.3, P-value<0.001) while four provinces had decreased mortality rates (AAPC: -16.6 - -1.0, P-value<0.001).

In 2012, the ASMR in Black population group was 5.7-fold higher than in the White population group. The highest mortality was recorded in Mpumalanga Province (19.8/100,000) and the least in the Eastern Cape Province (8.9/100,000). From 2000 to 2009, the ASIR of adenocarcinoma of the cervix was relatively low (2.00 to 2.6 per 100,000 women) and stable, while the incidence of squamous cell carcinoma was high (17.0 to19.0 per 100,000 women) and the rate increased by 1.4% annually. The relative survival rates were higher in White and Indians/Asian women (60-80%) than in Blacks and Coloureds (40-50%).

The results of the JCCCS studies showed that the association between CC and HIV infection increased from two-fold (adjusted odds ratio, (adjOR) =1.98; 95% CI: 1.34-2.92) during the pre-anti-retroviral therapy (ART) era (1995-2003) to three-fold (adjOR=2.94 95%CI: 2.26-3.83) in the ART era (2004-2010). Current tobacco smoking (adjOR=2.1, 95%CI: 1.10-4.01) and snuff use (adjOR=1.3, CI: 1.08-1.61) increased the likelihood of CC among Black women in South Africa. The risk of CC increased with prolonged use of hormonal contraceptives (P-value for trend = 0.003) and high parity (>6) (adjOR=4.5, 95%CI: 2.85-7.25).

The incidence and mortality of CC are probably underestimated due to underreporting of cancer in the country. South Africa had minimal changes in overall CC rates between 1994 and 2012, despite the initiation of a population-based CC screening program in 2000 and the nationwide roll out of ART in 2004. There was a marked disparity in CC rates by population group, age and province. HIV-infected women and those who use tobacco are more likely to develop CC, therefore targeted programs should be introduced to inform women about risk factors for CC. Maternal and child health initiatives should also involve CC control activities since a considerable number of women of the reproductive age (15 – 49 years) were affected.

Keywords: Cervical cancer, incidence, mortality, population group, South Africa, survival rate, trends

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ABBREVIATIONS AND ACRONYMS

AAPC	Average Annual Percentage Change
ADC	Adenocarcinoma
AdjOR	Adjusted Odds Ratio
AIC	Akaike Information Criterion
AIDS	Acquired Immune Deficiency Syndrome
APC	Age Period Cohort
ART	Antiretroviral Therapy
ASIR	Age-Standardised Incidence Rate
ASMR	Age-Standardised Mortality Rate
AUC	Area under the receiver-operator characteristic curve of a regression model
BIC	Bayesian Information Criterion
CC	Cervical Cancer
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CIN	Cervical Intraepithelial Neoplasia
CIR	Crude Incidence Rate
CMR	Crude Mortality Rate
HDI	Human Development Index
HIV	Human Immunodeficiency Virus
HLA	Human Leucocyte Antigen
HPV	Human Papilloma Virus
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
ICD-O-3	International Classification of Diseases for Oncology
ICPD	International Conference on Population and Development
JCCCS	Johannesburg Cancer Case-Control Study
LMICs	Low and Middle-Income Countries
MR: IR	Mortality to Incidence rate ratio
NCR	National Cancer Registry
PBCCS	Population Based Case-Control Studies

PLWHA	People Living With HIV/AIDS
SADC	Southern African Development Community
SCC	Squamous Cell Carcinoma
SDGs	Sustainable Development Goals
SEER	Surveillance Epidemiology and End Result
SSA	Sub-Saharan African Country
Stats SA	Statistics South Africa
TSG	Tumour Suppressor Gene
VIA	Visual Inspection with Acetic acid
VIF	Variance Inflation Factor
VILI	Visual Inspection with Lugol's iodine
WHO	World Health Organisation

DEFINITION OF TERMS

Population group	The apartheid government in South Africa grouped South Africans into Blacks, Whites, Indians/Asians and Coloureds (mixed ancestry) based on their ancestry. The 2011 census in South Africa also utilised this same groups to classify South Africans
Reproductive age	The period between initiation and cessation of menstruation which corresponds to the period that women can naturally get pregnant. The reproductive period in women is stated to be from 15 years to 49 years by the World Health Organisation.
Snuff	An addictive substance or powder that is produced by grounding dry tobacco leaf. It is usually inhaled or sniffed by users.

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1 CHAPTER ONE

INTRODUCTION

This chapter describes the global and national burden of cervical cancer (CC) and states the relevance of the study to policy makers in South Africa. Relevant literature was reviewed on the trends and determinants of CC, especially in South Africa. The chapter was concluded by stating the objectives of the study.

1.1 Background

Cervical cancer (CC) is a largely preventable disease, yet the global incidence is high: approximately 528,000 cases in 2012, with about 80% of the cases occurring in Low and Middle-Income Countries (LMICs) (1,2). In 2012, the estimated age-standardised incidence rate (ASIR) in the Eastern, Southern, Middle and Western African regions were 42.7, 31.5, 30.6 and 24.2 cases per 100,000 women, respectively (2,3) compared to 5.5, 4.4 and 6.3 per 100,000 women in Western Asia, Australia/New Zealand and Northern American regions respectively (1,2). CC is ranked globally as the fourth most common cause of cancer deaths in women and the second cause of cancer deaths behind breast cancer in Africa (2). Also, CC was responsible for about 267,000 global deaths in 2012. In South Africa, the ASIR and age-standardised mortality rate (ASMR) for CC were estimated to be 31.7 and 18.0 per 100,000 women respectively in 2012 as opposed to 4.3 and 1.0 per 100,000 women respectively in a high-income country like Finland (1).

Despite the relatively low incidence and mortality rates in most high-income countries, the CC incidence and mortality trends are still falling in those countries in contrast to the upward trends in most LMICs (4–6). This disparity in trend is because most high-income countries have well-entrenched prevention programs such as widespread screening programs, and improved oncological care as opposed to most LMICs that have poor screening programs, high burden of human immunodeficiency virus (HIV), harmful reproductive practices and dysfunctional health systems (2,5,7,8). Most of the countries in the Middle East and the Mediterranean region also recorded low and decreasing incidence rates of CC because of the prevalent cultural and religious precepts against extra-marital sexual relationships (2,4).

1.2 Problem statement

There are high rates of CC in South Africa despite the current efforts to reduce its incidence and mortality (9–11). In 1994, the International Conference on Population and Development (ICPD) stated that sexual and reproductive health (including CC management) should be a human right (12). However, most countries in SSA concentrated on the prevention of maternal and perinatal mortality but neglected reproductive health cancers (5,7,10).

The South African government instituted a CC population-based screening program in 2000 (9) and vaccination of school girls against Human Papilloma Virus (HPV) in 2014 (11). Resources have also been invested towards the control of human immunodeficiency virus (HIV) infection and tobacco smoking which are risk factors of CC (9,13–15). It is expected that these measures would impact on the temporal trends in the risks, incidence, morbidity and mortality of CC in South Africa (1,2).

Currently, there is a paucity of published data with robust analysis of the trends and predictors of the incidence and mortality of CC in South Africa. Previous studies on CC in South Africa were either hospital based, or conducted to monitor only trends in the mortality rates without evaluating the incidence rates (16,17). The last published trend study on CC mortality in South Africa was conducted about twenty-two years ago (1994) and the study excluded Black women because of the paucity of data (16). Also, the previous study may not represent the current situation of CC in South Africa.

1.3 Justification of the study

South Africa is currently undergoing demographic and health transition that mirrors the high-income countries (18). Also, there has been a shift in the morbidity and mortality related to HIV infection, largely after the nation-wide roll-out of anti-retroviral therapy (ART) in the country in 2004 (10,14,19,20). It is important to document the baseline incidence and mortality of CC in South Africa in order to track the progress of initiatives aimed at reducing the incidence and mortality of CC. Such programs include the CC vaccination program (11), HIV and smoking control programs (13,21) and the recently initiated Sustainable Development Goals (SDG 3 : Target 3.3: By 2030, end the epidemics of AIDS, tuberculosis, malaria, and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases and Target 3.4: By 2030, reduce by one-

third, premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being) (22). In addition, there is a need for studies that will highlight high risk and vulnerable groups of CC (23) in order to initiate targeted interventions.

Although, there are concerns about the quality of the national data on the incidence and mortality of cervical cancer in South Africa (2), it is still worthwhile to document the current trend and evidence based on available data so as to guide policy makers who are saddled with the responsibility of designing cost-effective prevention strategies (4,24,25). The World Health Organisation (WHO) encouraged member states to formulate locally relevant cancer control programs after reviewing evidence from their locality (4,24–27). To obviate the uncertainties related to data quality, we conducted a triangulation study, over a 19 - year period (1994-2012), of two national datasets and an established large hospital-based cancer case-control study with more than 10,000 female participants. Therefore, this study evaluated the trends and determinants of the incidence and mortality of CC in South Africa to provide empirical information to aid prevention of CC in South Africa.

1.4 Literature review

1.4.1 Pathology of cervical cancer

The Human Papilloma Virus (HPV) is a necessary (but not a sufficient) cause of CC (8,28–30). Most HPV infections are sexually transmitted, and the virus is usually spontaneously cleared by the body (29,31). However, about 2% of infection by 'high risk' (or oncogenic) strain of HPV persists in the cervix to cause premalignant and malignant lesions (8,29). The common high-risk HPV includes HPV 16,18,31,33,35,45,52 and 58 (29). Cervical HPV persistence causes viral oncoproteins (E6 and E7) to impair the anti-neoplastic activity of oncogenes (P53 and retinoblastoma (Rb)) (32). This leads to distortion of the nucleo-cytoplasmic ratio of cervical cells to form pre-malignant lesions known as cervical intraepithelial neoplasia (CIN) (4,28,29,31). The severity of the pre-malignant state depends on the degree of distortion of the nucleo-cytoplasmic ratio of the cervical cells. Further, CIN can progress from low-grade (CIN1) to high grade (CIN3) lesions (31,33). The latter is also known as carcinoma *in situ*. While CIN3 is the pre-malignant state of squamous cell carcinoma (SCC) of the cervix, adenocarcinoma *in situ* is a pre-malignant state of adenocarcinoma (ADC) of the cervix (33).

Premalignant state of the cervix is diagnosed through cytology or histology (34). The histological diagnosis is the CIN grades while the cytological classification is the Bethesda classification (34). For the Bethesda classification, the premalignant state of the squamous cell neoplasia is mainly classified in order of severity as: atypical squamous cells (ASC), low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL). The glandular cell types include Atypical cell types and endocervical adenocarcinoma *in situ* (34).

1.4.2 Histological types of cervical cancer

The two major histological types of CC are SCC and ADC (8,29,35). About 90-98% of CC cases are SCC while ADCs constitute about 2-10% of cases (8,29,35). SCC develops from the epithelial (surface) layer of the cervix (29,35) and is therefore easily available to screening procedures like the Papanicolaou (Pap) smear (29,35). Whereas, ADC usually arises from the glandular part (inner endocervix) of the cervix and may not be easily accessible (8,35–37). However, there are other less significant histological types of CC.

1.4.3 Conceptual framework of the incidence of cervical cancer

The Social Ecological Model (SEM) (38) stated that the determinants of a disease like CC are multi-factorial and such factors are inter-related at multiple levels. SEM further stated that such factors occur at the individual, relationship, community and societal levels (38). A simple conceptual framework of the multi-level aetiological factors of cervical cancer as shown in Figure 1.1 was proposed based on the available variables in the datasets.

Population group, age, educational attainment, marital status and province of residence can affect the incidence of HIV infection, smoking rate and sexual and reproductive behaviours and these, in turn, can impact on HPV persistence which sets up the cascade of events leading to cervical cancer (30,39). Also, population group, age, educational attainment, marital status, province of residence are directly associated with HPV persistence and CC (30,39). Thus, these latter factors are confounders in the risk of CC (40). Screening practices should ultimately reduce the incidence of CC (broken line in Figure 1.1).

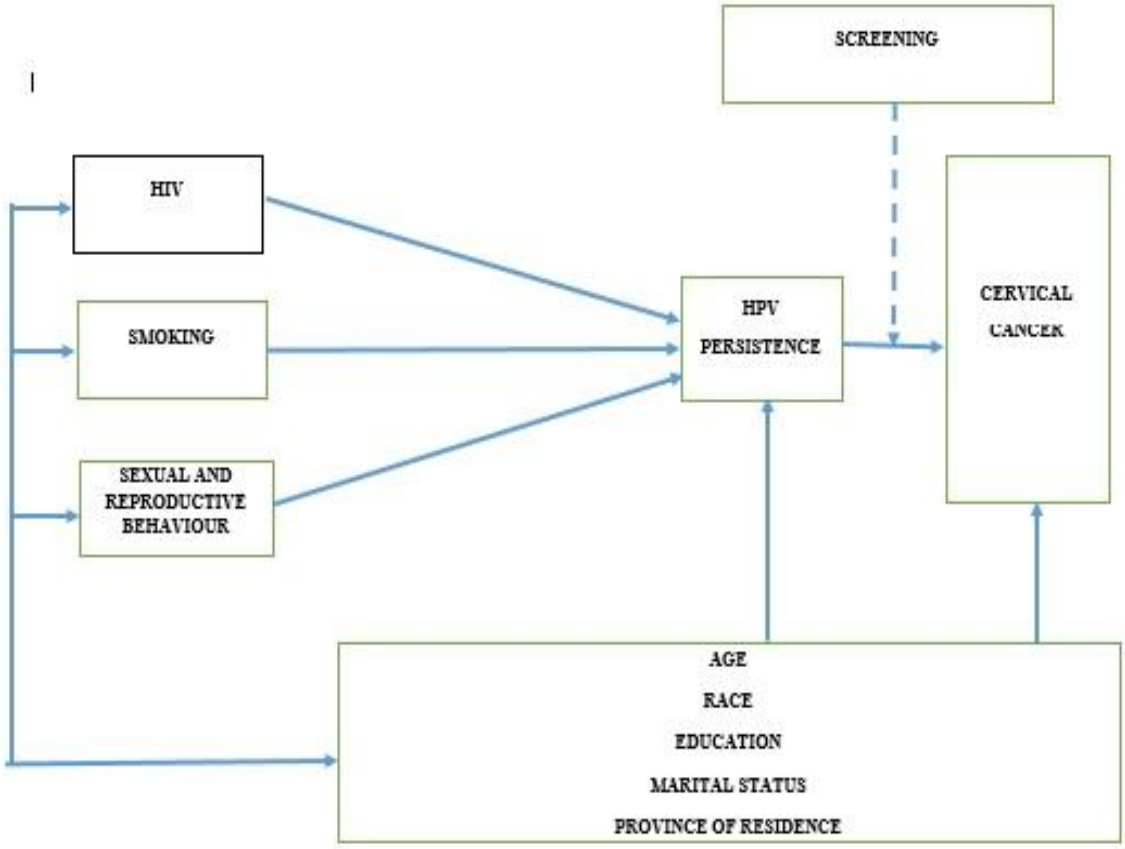

Figure 1. 1: Conceptual framework of multi-level determinants of cervical cancer in this study using the Social Ecological Model (SEM)

1.4.4 Risk Factors for Cervical Cancer

1.4.4.1 Population group and socio-economic status

Racial disparities in the incidence and mortality of CC has been reported in many countries (16,23,41,42). A study in the Netherlands showed that the likelihood of CC was about 8-fold higher in municipalities with a larger proportion of immigrants who usually have low socioeconomic status (23). Singh et al. (43) also found that the human development index (HDI) of countries can explain more than 52 percent of the variation in the global incidence and mortality of CC. Thus, the socio-economic status of individuals and nations can considerably impact on the incidence and mortality of CC in that country.

1.4.4.2 Age

The peak age of incidence of CC is 52-60 years in South Africa, Nigeria, Korea and England (30,44–46). However, the peak age of CC among people living with HIV/AIDS (PLWHA) was between 35 and 40 years before the advent of ART (30,45,47). Between 1970 and 1990, there was a decline in mortality rate among White South Africans aged between 35 to 64 years (16), while those younger than 35 years had lower and stable mortality rates for the same period (16). However, studies from Europe found that there was a decrease in the incidence and mortality of CC among women between 35 and 64 years during similar periods, but there was a gradual increase in the rates among younger women (48,49). These increased rates among young women in Europe were attributed to increased prevalence of ADCs and risky sexual behaviours (48,49).

1.4.4.3 Genetic predilection

Emerging evidence has shown that HPV clearance may not be effective if certain genes which regulate some aspects of the immunologic process are defective. Some of the implicated gene includes IL-1B, IL-10, CTLA4, human leukocyte antigen (HLA) class II DQB1, DQA1, DRB1 (32,50–52). Usually, the human host stimulates immune reactions after HPV infection (32) and such inflammatory processes then stimulate the expression of HLA type II and other genetic components to aid the tumour suppressor gene (TSG) in clearing the HPV infection (32). However, some women have a poor expression of HLA and other related genes thereby making the TSG ineffective in clearing the virus. The eventual persistence of the HPV can initiate the pre-malignant and malignant CC states (32,50).

1.4.4.4 Place of residence

It was shown that women living in rural areas in Mexico were more likely to develop CC than women living in urban areas (53). This is because most rural women may not be economically empowered or aware of CC screening opportunities (29,53). In contrast, a higher incidence of CC was found in urban areas in the Netherlands (23). This finding was linked to the prevalence of a more permissive sexual behaviour in the urban areas of the country (23).

1.4.4.5 Depressed Immunity (Human Immunodeficiency Virus infection)

In 1993, based on epidemiological studies, CC was designated as an AIDS-defining illness by the Centers for Disease Control and Prevention (CDC) (54–56). In high-income countries, the risk of CC among HIV-positive patients was more than five times higher than in HIV-negative patients (54,55,57). However, most early studies in Africa (including South Africa) showed lower risk ratios of between 1.5- and 2.6- fold of CC among HIV positive patients (30,44,57,58). Since HIV and HPV infections are sexually transmitted, HIV-positive patients, therefore, have a higher risk of acquiring HPV infections as compared to HIV-negative women (54,55,57). Also, PLWHAs have defective immunity, and hence they have increased the risk of having persistence of high-risk HPV than HIV-negative women (54,59,60).

HIV was a competing risk of death for CC before the general roll-out of anti-retroviral therapy (ART) in South Africa in 2004 (19,20,61). Thus, PLWHAs might have died from opportunistic infection before the evolution of CC in them. Although ART reduced the incidence and progression of pre-cancerous CC lesions among PLWHA (62,63), the prevalence of CC appears to increase despite access to ART in SSA (59,60,64,65). This is because ART improves the quality of life of PLWHA and increases longevity, thereby predisposing PLWHA to CC at old age (since they still have chronic defective immunity) (44,60). Thus, knowledge of the current impact of HIV infection on CC risks in South Africa during the ART era is imperative to inform policy makers (59).

1.4.4.6 Tobacco and alcohol use

The International Agency for Research on Cancer (IARC) designates tobacco smoking as a carcinogen for CC (31). The risk of CC among smokers is about two-fold greater than in non-smokers, and there is a dose-response gradient between tobacco smoking and CC (39,66–68). The previous report from the JCCCS study (1995 - 2004) found an increased risk (odds ratio of 1.5) of CC among smokers (13). However, little is known about the current impact of tobacco control programs in South Africa. High concentrations of nicotine in the cervical mucus of smokers are believed to aid the persistence of HPV in the cervix (69). Studies have also shown that there is an association between tobacco smoking and SCC, but no similar relationship has been found with ADC (67,69,70). Also, smokeless tobacco such as snuff (ground tobacco leaves that are inhaled/sniffed), can cause increased

risk of CIN and CC (71,72). However, this association has not been evaluated in South Africa.

There are conflicting reports on the association between alcohol consumption and the risk of CC (68,73). An increased risk of CC in women that abuse alcohol may be related to a higher likelihood of risky sexual behaviour and tobacco smoking among them (68,73). However, the association between alcohol and CC may be related to the genetic differences in metabolising alcohol (74). Thus, local studies on the relationship between alcohol and CC are necessary for South Africa.

1.4.4.7 Sexual behaviour

Since HPV is mainly a sexually transmitted infection, certain sexual behaviour plays an important role in its transmission and persistence in the body. Sexually transmitted infections such as chlamydia, gonorrhoea and herpes have been associated with HPV infection and CC (29,31,48,66,75). CC risk was found to be low in those who had late sexual debut (30,76,77). Thus, debut before the age of 17 years, and between 17 and 21 years was 2.3- and 1.8-fold, compared to women whose sexual debut was after 21 years of age (77). Thus, debut before the age of 17 years, and between 17 and 21 years was 2.3- and 1.8-fold higher compared to women who had sexual debut when they were older than 21 years (77). The risk of CC also increases with increasing numbers of sexual partnerships (4,30,76,77). However, there may be some bias in quantifying this factor as some women may not want to disclose the number of sexual partners they have had because of the social undesirability of multiple sexual partnerships (30,78).

Male circumcision may reduce the risk of CC in female partners compared to uncircumcised men (75). The South African government is currently promoting voluntary medical male circumcision as a primary preventive program for HIV transmission. An additional benefit of this program may be the reduction in the incidence of CC in the country.

1.4.4.8 Reproductive behaviour of women and cervical cancer

In a meta-analysis of 21 studies of CC risks and sexual and reproductive behaviours, the risk of CC among women who had their first pregnancy before their 17th birthday was almost

double that of women who had their first pregnancy at or after 25 years (OR = 1.77) (76). Also, CC risk has been shown to increase with increasing parity (29,76,79–82).

1.4.4.9 Contraception

Consistent male condom use can reduce the risk of HPV transmission by about 70% (83). However, use of oral and injectable contraceptives can increase the risk of CC by two-fold (28,84,85). However, some authors found no association between oral contraceptive usage and CC (39). Although HIV infection and hormonal contraceptives can have a synergistic effect on the evolution of CC, the risk did not increase among a small cohort of HIV-positive patients on hormonal contraceptives in South Africa (86). Also, smoking was believed to potentiate the risk of hormonal contraceptives on CC evolution (69,84).

1.4.5 Prevention of cervical cancer

The four levels of prevention of CC include the primordial, primary, secondary and tertiary preventive methods (33,87–89). Trend analysis of the incidence and mortality of CC is useful in assessing the impact of preventive care in a country.

Primordial prevention includes programs or policies that reduce underlying socio-economic and cultural milieu that increase the prevalence of CC (89). Such interventions include promotion of racial equality and equity in South Africa, eradication of poverty, encouraging girl child education; promoting gender equality and women empowerment; provision of health insurance (or free medical care for women) and strengthening health systems in the country. Since the advent of multi-racial democracy in South Africa in 1994, there have been ongoing efforts to implement the preceding interventions as stated in sections 1.2 and 1.3 above (10,18,90). The South African government is in the process of fully implementing the National Health Insurance (NHI) scheme that would engender universal health coverage (91) which will improve access to reproductive health services.

Primary prevention methods are programs designed to prevent the acquisition, transmission and persistence of HPV in order to reduce the risks of CC. This includes initiatives aimed at a reduction in: risky sexual practices, fertility rate, early marriage, teenage pregnancy, HIV prevalence and tobacco smoking and increased male circumcision rate (9,33,75). Furthermore, the immunisation of pre-pubertal girls and boys with the HPV vaccine before sexual debut (11,29,42) is a primary preventive strategy. A randomised controlled trial has

shown that the vaccines can prevent about 70%-95% of CC cases (4,11,29). There are three vaccines that are currently approved. They are bivalent, tetravalent and nanovalent vaccines that are targeted at HPV 16, and 18; HPV 6,11,16 and 18 and HPV 6, 11, 16, 18, 31, 33, 45,52, and 58 respectively (34).

The oldest method of secondary prevention of CC is the screening of women with the aid of Papanicolaou (Pap) smear (4,92,93). Women diagnosed with pre-cancerous lesions after Pap smear are treated and monitored to prevent the development of CC (33,80,92). Although there are concerns about the use of case-control studies to evaluate screening outcomes (94), nonetheless, Pap smear was found to reduce the risk of CC in a case-control study in South Africa (94,95). Population-based Pap smear screening is not common in SSA because of its cost to the health system (33,80,92). However, opportunistic screening which occurs during post-natal visits and gynaecological consultations are more common (79,90). There is the suspicion that the incidence of ADC is not decreasing as fast as SCC in high-income countries because of increased permissive sexual behaviour and poor detection of ADC by Pap smear (35). South Africa instituted a population-based CC screening program in 2000, aimed at offering free CC screening services to women between the ages of 30 and 50 years at an interval of 10 years (9). It has been 16 years (2000-2016) since the initiation of the cervical cancer screening program. A study on the trend analysis of the incidence and mortality of CC is, therefore, necessary to review the impact of the program so far.

Visual inspection of the cervix with acetic acid (VIA) or with Lugol's iodine (VILI) has been recommended to replace Pap smear in the LMICs like South Africa (33,92,96,97). Clients can know the result of the VIA test immediately and can be offered treatment as soon as possible (33,92,96,97). It was found that VIA was the least costly as compared to Pap smear and HPV deoxyribonucleic acid (DNA) testing among PLWHA in South Africa and it requires less skill (33,98). VIA was also shown to have comparable sensitivity as Pap smear in detecting CIN among HIV-positive women (60,98). However, South Africa currently has no national policy on the deployment of VIA or VILI (9,33,92,96,97). Typing of high risk HPV DNA genotypes can improve the sensitivity of detecting the cervical pre-malignant state, especially for ADCs and has been recommended for general deployment after considering its cost-effectiveness (29,35,92,99).

Tertiary prevention of CC encompasses the various treatments that are offered to the CC patients to effect a cure, and reduce complications and progression of the disease (33,100–102). Provision of

oncological surgeries for early disease, radiotherapy services, hospice, pain management, psychological support or other palliative care is important aspects of tertiary prevention (33,102). Most high income countries have good primary, secondary and tertiary prevention programs of CC and therefore have low rates of the disease (33,102,103). However, most LMICs have poor primary, secondary and tertiary prevention strategies and thus have high CC rates (57,59,96,103).

1.4.6 Statistical and epidemiological methods

1.4.6.1 Trend in survival rates

In high income countries, the 5-year survival rate of CC is as high as 60-80%, but it is less than 45% in most LMICs (29,42,96,100,103). The lower survival rates in LMICs is because patients present late for treatment, at an advanced stage of the disease, and there were inadequate oncology services which led to long waiting time for treatment. Also, there may be poor recognition of early signs of cancer by health practitioners (29,96,103,104). To conduct relative survival analysis from CC data, cancer patients must be followed-up, or there must be an adequate linkage of the cancer registry to the vital statistics registry so as to monitor when death occurred (41,105,106). But these facilities are not common in South Africa. Thus, the usual survival analysis methods (actuarial method, Kaplan-Meir, Cox proportional regression) cannot be easily utilised for evaluating survival rates in South Africa (41,105,106).

Vostakolaei and co-workers validated the complement of "mortality to incidence rate" ratio (1-(MR: IR)) as a proxy for the 5-year relative survival rate of CC (105). Although the ratio has not been validated in LMICs, it was recommended that it can still be used for evaluating survival rates of CC in countries with poor record linkages (105). This present study utilised the complement of MR: IR (1-(MR: IR) to estimate the overall and racial 5-year relative survival rates of CC in South Africa.

1.4.6.2 Other statistical and epidemiological methods

Descriptive methods have been utilised to study temporal trends and regional variation of cancer incidence and mortality (4,16,107). Comparison of cancer trends among population groups, age groups and regions are conducted with the aid of analytic tools like the average annual percent change (AAPC), joinpoint regression analysis and age period birth cohort (APC) analysis (22,43,53,108).

Case-control, nested case-cohort and cross-sectional studies are the usual designs for epidemiological cancer research (28,55,66,109). However, case-control studies are the commonest study design for cancer research because of the extended latency period of cancers (109). The most common case-control studies are population based case-control study (PBCCS) and a hospital based case-control study (HBCC) (109).

Population-based case-control studies are study designs in which the cases and controls are recruited from a geographically defined area over a specified period (109,110). A well conducted PBCCS should not have selection and information bias but such studies are usually expensive to conduct (109). In the HBCC, the cases are the cancer cases diagnosed in the hospital, and the controls can be other cancer types that were diagnosed in the hospital or other patients, healthy relations or visitors to the hospital (109). Selection, information (or recall) or referral bias may occur among cases and controls (85,109). Therefore, some researchers utilised other cancer patients that were diagnosed at the same hospital as controls to obviate these potential biases (13,45,85). The controls did not have the same aetiological risk factors as the cancer case that was being investigated. This is important so as to be able to properly ascertain the excess risk of the cancer under investigation (45,85). This method was utilised for analysing the risk factors of CC using the Johannesburg Cancer Case-Control Study (JCCCS) in this report (13,45,85).

1.5 Research question

What are the trends and determinants of the incidence and mortality rates of cervical cancer in South Africa (1994- 2012)?

1.6 Research hypotheses

Three research hypotheses have been proposed as stated below.

Null Hypothesis 1: The trends in overall incidence and mortality of cervical cancer was stable during the period 1994 - 2012 in South Africa

Alternate Hypothesis 1: The trend in overall incidence and mortality of cervical cancer significantly changed during the period 1994 - 2012 in South Africa.

Null hypothesis 2: There was no significant difference in the trends in incidence and mortality of CC within the provinces and among population and age groups, during the period 1994 – 2012 in South Africa.

Alternate hypothesis 2: There was a significant difference in the trends in incidence and mortality of CC within the provinces and among population and age groups, during the period 1994 – 2012 in South Africa.

Null hypothesis 3: There was no association between cervical cancer and HIV infection, tobacco smoking, alcohol abuse and reproductive behaviours of Black South African women between 1995 and 2010.

Alternate hypothesis 3: There was an association between cervical cancer and HIV infection, tobacco smoking, alcohol abuse and reproductive behaviours of Black South African women between 1995 and 2010.

1.7 Research objectives

Aim

This study aimed to determine the trends and determinants of the incidence and mortality rates of cervical cancer in South Africa between 1994 and 2012.

Specific Objectives

The specific objectives of this study were:

1. To determine the temporal trend in the crude and age-standardised incidence rates (CIR, ASIR) of cervical cancer by population group, age group and histological type in South Africa from 1994 to 2009 using NCR data.

2. To determine the temporal trend in the crude and age-standardised mortality rates (CMR, ASMR) of cervical cancer by population group, age group and province in South Africa from 2004 to 2012 using Stats South Africa data.

3. To determine the trend in the national 5-year relative survival rate ((1-MR: IR) of cervical cancer among the racial groups in South Africa between 2004 and 2009 using results obtained in Objectives 1 and 2 above.

4. To evaluate risk factors for cervical cancer among Black South Africans in Johannesburg between 1995 and 2010 using the Johannesburg Cancer Case-Control Study.

2 CHAPTER TWO

METHODOLOGY

2.1 Chapter Overview

This chapter briefly describes the demography of South Africa, the study settings, designs, populations and sampling methods of the various arms of this research. Data management and analyses that were conducted for each of the three study arms were also described.

2.2 Demography of South Africa (study setting of the research)

South Africa is a multi-racial middle income country with a total landmass of about 1,220,813 square kilometres (111). The estimated population of South Africa in 2015 was 54.96 million, and about 51% were females (112). In 2015, the proportion of the female by population group was: Blacks (Black Africans) (80.4%), Coloureds (mixed ancestry) (8.9%), Whites (European descent) (8.3%) and Indians/Asians (2.4%) (111,112).

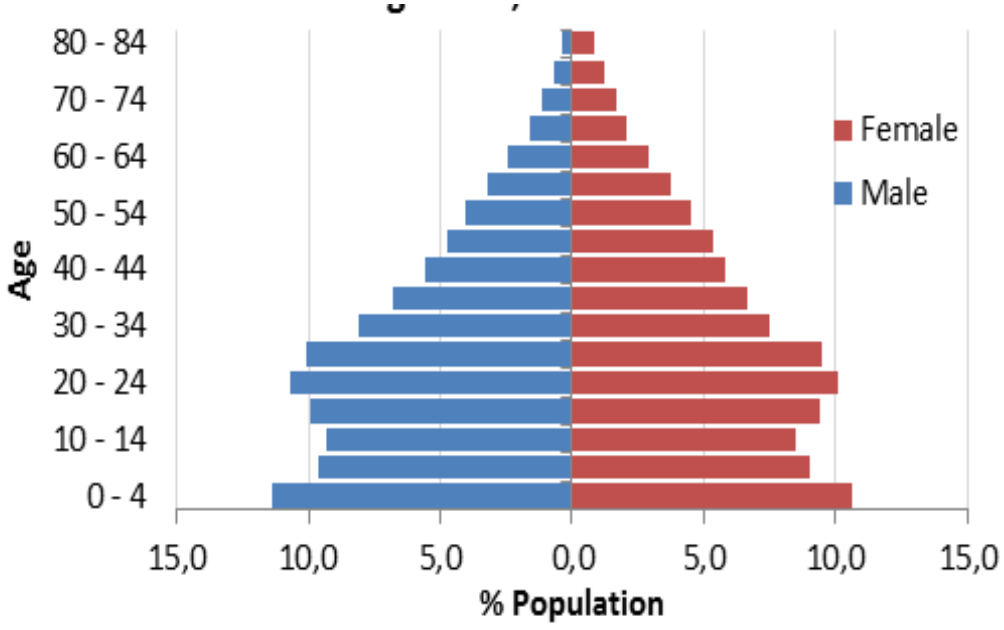

Figure 2. 1: Population structure of South Africa in 2011 (111,113).

The country is currently divided administratively into nine provinces of Eastern Cape (EC), Free State (FS), Gauteng (GP), KwaZulu-Natal (KZN), Limpopo (LIM), Mpumalanga (MP), Northern Cape (NC), North West (NW) and Western Cape (WC) (111,112). Each of the provinces has a varying number of district municipalities and local municipalities (111–113). In 2015, the life expectancy at birth for females was 64.3 years. The population pyramid of the 2011 census as shown in Figure 2.1 above depicts the age structure of the South African population, with the age group 0-4 and 15 – 24 comprising the largest proportion (111,113).

2.3 Study design

This study was a secondary data analysis of three datasets. We conducted temporal trend analyses on the NCR (1994-2009, 16-year period) and Stats South Africa (2004-2012, 9-year period) datasets. We further designed three unmatched case-control studies from the JCCCS based on three major risk factors of CC. The risk factors were (I) HIV infection (45) (II) tobacco smoking and alcohol (13,66,67) and (III) sexual, reproductive and hormonal factors (28,76,82,84,85).The three case-control studies were necessary to properly characterise the risk factors of CC because the cancer controls should not have similar risks as the risk under considerations (13,85) (section 1.4.6.2 above). Thus, the control arms of the three JCCCS sub-studies were selected by excluding any cancer site(s) that was/were associated with the risk factor under consideration as was previously conducted (13,45,85). Furthermore, we cannot use a single or combined logistic regression model for the analysis of JCCCS because each of the major risk factors under consideration has a different set of cancer controls. See Table 2.1 below.

2.4 The setting of the study arms:

2.4.1 The National Cancer Registry (NCR)

The NCR was established in 1986 as a pathology-based national cancer surveillance system with the aim of passively collecting all cancer cases that were diagnosed pathologically by the private and public pathology laboratories in South Africa(114–118). There were concerns that private laboratories did not adequately report cancer cases to the registry from 2005 to 2007 because they were worried about the confidentiality of their patients' records (114). In 2011, the South African Government enacted a law, which made cancer diagnosis a notifiable disease so as to improve cancer reporting in the country (114,116). The cancer registry has information about the age at diagnosis,

population group of the patient, date of diagnosis, hospital name, province of diagnosis and the histological diagnosis (114,116,117). Routine review of the data is conducted by NCR staff to remove double entry, and Hot-deck imputation method is used to fill missing population groups (114,116,117)

2.4.2 Statistics South Africa (Stats SA)

Stats SA is the national agency shouldered with the responsibility of organising population census and collection of official national data on mortality in South Africa (112). The mortality data were collected from the records of notification of death that were available at the Department of Home Affairs (112). Experienced coders at Stats SA code the cause of death according to the International Classification of Diseases, tenth revision (ICD-10) (119). Data was made available by Stats SA on request.

2.4.3 Johannesburg cancer case-control study (JCCCS)

The JCCCS is an ongoing cancer case-control study conducted by the NCR that recruits consenting Black cancer patients before treatment at the greater Johannesburg public referral hospitals (13,85,120,121). The JCCCS study aims to evaluate the impact of environmental and lifestyle risks on the evolution of cancers among Black South Africans (85). The study focuses on Blacks because they were the historically underserved with scanty prior research conducted among them (85). The cancer cases that were recruited into the study were mostly pathologically confirmed (13,85,120,121). Trained nurses interviewed the recruited patients in English or their local language with the aid of a structured questionnaire and collected blood and serology samples (13,85,120,121). The study commenced in March 1995 and continued till date. We analysed data from March 5, 1995, to 31 December 2010. HIV screening was conducted for all consenting participants. Since there are few exploratory variables in the NCR surveillance dataset (sexual and reproductive factors including HIV status were not captured by the NCR data), and the Black population constitutes about 80% of the South African population (112), we utilised another dataset, the JCCCS data to further characterise CC risk.

2.5 Target and study population (outcome and exposure variables)

The target population for the study of CC incidence and mortality trends was the female population (aged ≥ 15 years) of South Africa since the two datasets that were used for this aspect of the study were national datasets. (However, there may be some concerns about

quality of data as discussed under strength and limitations of the study in sections 4.4 and 4.5 below).

However, the target population of the study of CC risk factors of the JCCCS was all Black South African women, since the greater Johannesburg public referral hospitals have the largest oncology facility in the country and receive and treat patients from all provinces of the country. The JCCCS is an ongoing study among Blacks (85).

2.5.1 Incidence and mortality data from NCR and Stats SA

2.5.1.1 Study population:

The study population consisted of all women with newly diagnosed cases of CC in the NCR dataset from 1994-2009 and all women who died from CC as captured by the Stats SA dataset from 2004-2012.

2.5.1.2 Outcome variables: CC cases (ICD-O-3: Code C53) and mortality (underlying cause of death: ICD-10, C53), respectively.

2.5.1.3 Explanatory variables:

The explanatory variables were

1) Incidence data: age at diagnosis, population group, year of diagnosis, histological diagnosis, type of laboratory of diagnosis, topography/anatomic site of neoplasm.
2) Mortality data: age at death, year of death, population group, smoking history, usual province of residence, marital status, educational attainment of the deceased and the health institution where the patient died.

2.5.2 Cervical cancer risk factors in the JCCCS Data (1995-2010)

2.5.2.1 Study population:

All female cancer patients in the JCCCS from 1995 to 2010 (16 years) were the study population.

2.5.2.2 Selection of cases and control.

Cases included all participants who had CC and controls were participants with the cancer sites that were not related to the risk factors of interest (45,85).

2.5.2.3 Eligibility criteria

Inclusion criteria:

For the three sub-studies, the inclusion criteria for the cases and control were the same:

Cases: All CC cases aged 18 years or older in the JCCCS between March 1995 and December 2010.

Controls: All the other female cancer cases aged 18 years or older in the JCCCS between March 1995 and December 2010.

Exclusion criteria:

Cases: There were no exclusion criteria for the cases (CC).

Controls: While selecting the controls for each of the case-control studies: (I) HIV (II) smoking and alcohol use and (III) sexual, hormonal and reproductive behaviours, we excluded from the each control arm, female cancer sites that were known to be associated with the risk factor under consideration as stated in Table 2.1 below. Furthermore, cancers with the ill-defined or unspecified site were also excluded.

Table 2. 1: List of excluded cancer sites for each control arm of the JCCCS dataset

Major risk factor for cervical cancer	Excluded cancer sites
HIV	anal, breast (please see explanation above) , conjunctival, eye, Karposi sarcoma, larynx, leukaemia, lung, non-Hodgkin lymphoma, oral, oropharyngeal, sarcoma, stomach, squamous cell cancer of the skin, tonsil, vagina and vulvar.
Tobacco smoking and alcohol use	anal, breast, bile duct, bladder, colorectal, hepatoblastoma, kidney, larynx, lung, melanoma, nasal, non-Hodgkin's lymphoma, oral, oesophageal, ovarian, pancreatic, pharynx, sarcoma, skin, stomach, vagina and vulvar.
Sexual, hormonal and reproductive factors	breast, biliary, bile duct, endometrial, bladder, fallopian tube, hepatoblastoma, Kaposi sarcoma, ovarian, placenta, vagina and vulvar.

Furthermore, patients with breast cancer were also excluded from the control arm of the three case-control studies because female breast cancer shares some aetiological associations with gynaecological cancers like CC and also have some association with smoking and alcohol (13,85,122). Also, breast cancer constitutes a high proportion of female cancer cases in the JCCCS (N=3,092, 44% of all female non-cervical cancer cases in JCCCS) and if we

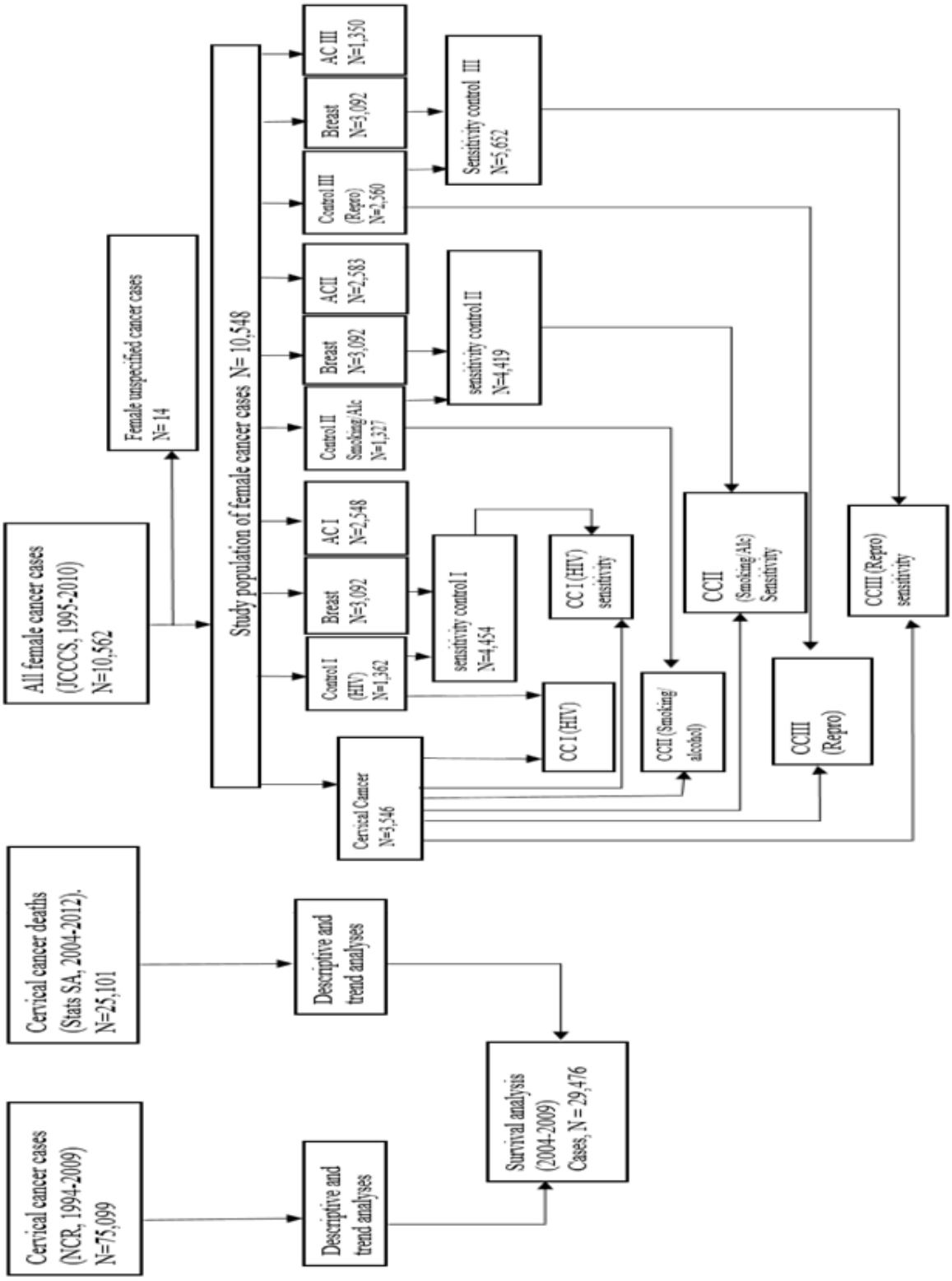

Figure 2. 2 Populations of the research arm

add it to the control arm of each case-control study, it can considerably tilt the point estimate thereby blurring the randomness of the control arm selection. Nevertheless, a sensitivity analysis was conducted for each sub-study by adding the excluded breast cancer patients to each control arm after which univariable and multivariable analysis was also conducted.

2.5.2.4 Study sampling and matching

Sampling was not conducted. Controls and cases were not matched.

Populations of the CC incidence, mortality and risk factors were as depicted in Figure 2.2 below. In all, 75,099 cases and 25,101 deaths were reported to the NCR and Stats SA from 1994 - 2009 and 2004 - 2012 respectively. Of these, 22,476 cases and 16,158 CC deaths from 2004 to 2009 were utilised for relative survival analysis. The three case-control sub-studies (and sensitivity analyses) included 10,548 female cancer participants in the JCCCS study, after excluding 14 patients that had unspecified cancer site.

2.6 Data processing and statistical analysis

2.6.1 Data extraction and quality control

Anonymised datasets were obtained from NCR, JCCCS and the Stats SA. Each data set was reviewed for missing values, consistency and outliers using appropriate Stata commands. Duplicates were also checked, and no duplicate was found. Continuous variables were assessed for normality.

2.6.2 Variables and coding of Stata SA and NCR datasets.

The Stats SA and NCR datasets have such categories as ‘unknown’, “unspecified”, “did not answer”. These responses were coded as ‘missing’ and included as a category in the analysis. The data management is as stated below:

Age: was defined as the age at diagnosis in the NCR data and age at death in the Stats SA data. It was considered as a continuous variable or categorised into 5-year interval as commonly done in cancer research (109,110) and for standardisation. Age was also categorised into a contextually relevant binary variable of “<50” and “≥ 50” to represent women within and beyond the reproductive age groups respectively.

Population group: The population groups were 1=Blacks, 2=Coloureds, 3=Indians/Asians, and 4=Whites categories (112).

Marital status: This variable was in the Stats SA dataset and was coded as 0="never married/ single", 1=Married, 2=Widowed, 3=Divorced/Separated.

Smoking status: This variable was recorded in the Stats SA mortality dataset. The ascertained smoking status was coded as either: 1=No and 2=Yes.

Highest educational attainment was coded as 1=No education, 2=Primary school (9 years of education), 3=High School (14 years of education), 4=Tertiary (more than 14 years of education).

Year of diagnosis and year of death: This variable was coded as a categorical variable.

Province of residence: This variable was available in the Stats SA dataset only and 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.

Laboratory of diagnosis: Coded as 1= Government laboratory and 2= Private laboratory.

Topography/Anatomical site of the neoplasm**:** Coded as 1= Endocervix (C53.0); 2=Exocervix (C53.1); 3= Overlapping (C53.8), 4= Cervix uteri (C53.9).

The histological type of the cervical cancer: The ICD-O-3 codes that were provided in the NCR dataset were re-coded according to the IARC classification (35) : 0=SCC: 8050-8078, 8083-8084; 1=ADC: 8140-8141, 8190-8211,8230-8231, 8260-8263, 8310,8380,8382-8384, 8440-8490, 8560-8569,8570-8574, 8576, 8560-8569; 2=OTHERS: all other codes.(35).

The institution of death: 1=Hospital, 2=Emergency room/outpatient, 3=Dead on arrival, 4=Nursing homes, 5=others, unspecified and unknown were coded as 6= "missing".

2.6.3 Variable analysis and recoding of JCCCS data

Type of residence: The type of residence was already coded as 1=urban, 2=rural based on criteria of classifying municipalities in South Africa as utilised by the NCR.

Age at first pregnancy was calculated by subtracting the 'age of first child' (either dead or alive) from the 'age at interview' (which was the presumed age at diagnosis). The variable was then recoded into an ordinal variable based on literature (77) to: 1 = "<17 years" , 2 ="17-20", 3 = "21 years and above".

Parity was coded as ordinal variable into: nulliparous 1 = (nil parity), 2 = "1-2 parity", 3= "3-4 parity", 4= "5 and above parity". Parity from 1-4 was traditionally grouped together as a category in the most previous literature (67,84,85). However, in this analysis, the parity

category of 1-4 was further divided into "1-2"; "3-4" because of the declining fertility rate among South African women (10,113).

Number of lifetime sexual partners was coded as ordinal categories of:1 = 0-1 partner , 2= 2-5 partners, 3 = >5 partners.

"Oral contraceptive use" was generated after combining and recoding two variables in the dataset: "ever had oral contraceptive" and "length of oral contraceptive use". The variable was coded into ordinal variable as 1 = 'never', 2 = "yes, (<5years)", 3 = "yes, (5-10 years)" and 4 = "yes (>10 years)". This was as previously conducted in the literature (84).

"Injectable progesterone contraceptive" was recoded as was done for "Oral contraceptive use" above (10,85).

"Ever had pap smear" was coded as a binary variable of 1 = "never" and 2 = "1 or greater" screen. Questions on Pap smear were introduced into the study in 2001 and those participants that stated that they had Pap smear test during the cancer illness (diagnostic Pap smear) were coded as not having done Pap smear before. The variable was not utilised for multivariable analysis since there was no information between 1995 and 2000 and therefore missing data was high (43.8%) (85).

Alcohol use was coded as ordinal variable as 1=never drink, 2=moderate drinkers (less than 8 drinks per week), 3=heavy/binge drinker (8 drinks and more in a week) (121).

Snuff use: was coded as ordinal variable as: 1=" never", 2="currently use" and 3="used in the past".

Smoking status: was classified as ordinal variable as 1=non-smokers, 2=ex-smokers, 3=current light smokers 4=current heavy smokers. Patients that stopped smoking within five years of cancer diagnoses were re-classified as "current smokers" because they might have stopped smoking because of their illness (85,121). Current smokers were further classified based on the number/amount of cigarettes, pipe or hand rolled tobacco they smoked per day. It is assumed that 1 cigarette or hand rolled tobacco or pipe is equivalent to 1g of tobacco (121). Thus, current smokers were further classified as light smokers, if they smoked between 1-14g/day and heavy smokers if they smoked more than 14g of tobacco per day (121).

Interviewers: Nine interviewers participated in the study so, the variable "interviewer" was included in the multivariable analysis (121).

Year of interview: Was assumed as the year of diagnosis and recoded into ordinal variable as 1 = 1995 – 2000, 2=2001 – 2005, 3=2006 – 2010. Age, educational qualification, marital status and province of birth were as previously described in section 2.6.2 above.

The variables were described and frequency analysis was conducted. Mean (±standard deviation (SD)) or median (Interquartile range), if not normally distributed, was reported for continuous variables. Complete case frequency analysis was also conducted for variables that had more than 50% missing data.

2.7 Objectives One and Two: Cervical cancer trend analysis of incidence (NCR) and mortality (Stats SA) data.

2.7.1 Crude rates

The annual crude incidence rate (CIR) was calculated for each year by dividing the annual CC cases by the mid-year population of females, aged ≥ 15 years (assumed as the person-year) as published by Stats SA. The annual CIRs per population group, age group and histological types were calculated from 1994-2009 (109,110,116). The age-specific incidence rate for the study period was calculated by dividing the cumulative number of cases in each five-year age category by the cumulative mid-year population of each category over the study period. All calculations were conducted in Excel (Microsoft 2010) and exact negative binomial regression (nbreg) estimation was conducted to confirm the calculations (nbreg was utilised because the data violated the assumptions of Poisson regression in that there was over-inflation, mean: variance ratio>2)

2.7.2 Population denominators

The mid-year populations from 1994 to 2011 were published by Stats SA except for 1994, 1995 and 2012. The mid-year population for 2012 was calculated from the population growth rate of 2011 as published in 2013 by Stats SA.

For 1994 and 1995, the formula for calculating intercensal increase which assumed a constant annual population growth rate was used (109,110,116).

There were population censuses in South Africa in 1996 and 2001 which was a period of 5 years. Thus, the annual intercensal increase between 1996 and 2001 was calculated using the formula below:

(2001 population – 1996 population) ÷ 5

This annual change was subtracted arithmetically from 1996 to get the mid-year population of the unavailable years (1994 and 1995).

2.7.3 Crude mortality rates (CMR)

Similarly, the crude mortality rate (CMR) was calculated from annual CC deaths obtained from the Stats SA dataset and the appropriate mid-year population from 2004 to 2012.

2.7.4 Age-standardised rates

Age-standardised rates were directly calculated for both incidence (ASIR) and mortality (ASMR) rates using the 1964 Segi's world population as standard population (2,107,108,113,114). The standardised rates were calculated by population group, histological types, age group and province of residence.

The provincial ASMR was presented on the map of South Africa with colour shading and mapping by the aid of the ARC GIS software after obtaining the geocodes of South Africa from the internet. Intra-provincial clustering analysis was not conducted because a province is too large for meaningful intra-class correlation. The provincial mortality rates were divided into three groups (tertiles) based on their magnitude.

2.8 Temporal Trend analysis: Average annual percent change (AAPC).

Average annual percent change (AAPC): This is a measure of the average change over the period of study (110,123,124). A linear regression was fitted for ln(rate) as the outcome variable and the calendar year as the explanatory variable (108,123,124).

The equation of the trend (108,123,124) is:

$\ln(Rate) = \beta \times (Calendar\ year) + C$.

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

Where, β= coefficient of the calendar year, e = 2.7 and C = Constant (or intercept)

The years 2015 (beginning of the SDGs) and 2030 (end of SDGs) were substituted in the trend equations to calculate the projected ASIR and ASMR for the year 2015 and 2030 respectively. The linear regression models were fitted for overall and by population and age groups, province of residence and histological types.

We multiplied the AAPC by the initial ASIR of 1994 to obtain an average change in cases per annum. Similarly, the average annual change in deaths per annum was obtained by multiplying the AAPC by the initial ASMR of 2004. Positive AAPC suggests an average

annual increase in rates while negative AAPC show average decline. AAPC between -0.5 and +0.5 suggest a stable trend (108).

Partitioned AAPC was calculated for: 1994-1998; 1998-2001; 2001-2009 and for overall ASIR and by population and age groups based on the visual inspection of the graphs of the trends because national cervical cancer screening commenced from 2000 and there was marked year to year variability in rates before 2000 (125). Similarly, portioned AAPC was calculated for mortality trends from 2004 to 2008 and from 2008 to 2012 respectively after visually inspecting the graphs of the trend.

2.9 Objective Three: Annual 5-year relative survival Mortality

The 'MR: IR' was calculated by dividing the CMR by the CIR (105). The 5-year relative survival rate was calculated by using the formula: 1 - (MR: IR) (105). This was multiplied by 100 to express the rate as a percentage. This calculation was also conducted annually by population group between 2004 and 2009, which was the overlapped time period between the incidence and mortality data. The change in survival rate over the 5 year calendar period was also calculated by subtracting the survival rate in 2009 from the survival rate in 2004 and dividing the change by the baseline rate of 2004.

2.10 Objective Four: Risk factors of cervical cancer among Black women in Johannesburg, South Africa

2.10.1 Use of vce robust option and model building.

The vce (robust) option was used to obviate any variation from the assumption of logistic and linear regression. The "vce (cluster province) would have been used to correct for any intra-provincial variations, but the NCR data did not have the province of residence of the cases and the overall Wald's P-value of the JCCCS model using the "vce (cluster province) did not display any value for some variable and multivariable model, (possibly because of small numbers of some province in the dataset) for us to decide if the model being built was statistically significant. Thus, a uniform analysis was conducted with the "robust" option for the three datasets. The standard errors of the vce (robust) option and the vce (cluster option) were very similar when compared in the mortality data (Stats SA data)

2.10.1.1 Univariable and Multivariable analysis of the three sub-studies of the JCCCS data

2.10.1.2 Socio demographic and sexual, reproductive and hormonal factors of all the female cancer patients in the JCCCS study from 1995 to 2010.

Categorical variables of CC patients and other female cancer patients were compared using Pearson's Chi-square test. Chi-square for trend was used to assess for trends for variables with ordinal categories. Student's t-test was utilised for comparison of the mean age among the CC patients and the other female cancer patients.

2.10.1.3 Univariable and multivariable analysis of cervical cancer risk factors from the JCCCS.

For the 3 case-control sub-studies of the risk factors of CC, the cases were CC patients and were coded as 1 and the appropriate control group was coded as 0.

2.10.1.4 Univariable analysis of the case-control studies.

Unconditional univariable binary logistic regression with the 'vce (robust)' option was conducted for each of the 3 case-control sub-studies utilising the individual explanatory variables as stated below.

2.10.1.5 Multivariable analysis of the case-control sub-studies from the JCCCS

The case-control study I (CC I: HIV as a major risk factor): The primary explanatory variable was HIV.

Case-control study II (CC II: Tobacco smoking and alcohol use as a major risk factor): The primary explanatory variables were Tobacco smoking and alcohol.

Case-control study III (Sexual, reproductive and hormonal factors): The primary explanatory variables were sexual, reproductive and hormonal factors.

For each case-control sub-study (CC I, II, III), multivariable unconditional logistic regression (stepwise forward regression) analysis with vce (robust) option was performed. Variables that were associated with the outcome (CC) after univariable analysis (P-value <0.2), were added sequentially to the multivariable model. For the HIV case-control (CC I) sub-study, further sub-analysis was conducted by restricting the analysis to the pre-ART era (1995 - 2003) and ART era (2004 - 2010) respectively. The comparison was made between the point estimates of HIV status for the pre-ART era and the ART era.

A sensitivity test was conducted by introducing "history of Pap smear" to the model of the ART era since the Pap smear information was introduced in 2000 (four years earlier than the ART era) and there was minimal missing data (1.2%) for Pap smear during the ART era. Also, HIV and smoking status are theoretically likely to interact with hormonal contraceptives (69,84,86). Thus, interaction term of HIV status and hormonal contraceptive was introduced into the model for CC I (HIV study) and another interaction term of smoking status and hormonal contraceptive was introduced into the model for CC II (smoking and alcohol risk)

Models with the lowest post estimation Akaike information criteria (AIC) and Bayesian information criterion (BIC) were taken as the best and parsimonious model. Some variables were determined *a priori*: HIV, smoking status and age. The Pearson's goodness of fit and then Hosmer and Lemeshow's goodness of fit test were conducted to measure the degree of fit of the data. A model to which the variables fit the data is expected to have a P-value >0.05. The area under the receiver-operator characteristic curve (AUC) of each regression model was also determined so as to evaluate the predictive value of the models.

The explanatory variables were HIV, Tobacco smoking, snuff use, alcohol use, age at diagnosis, marital status, educational attainment, province of residence, type of residence, oral contraceptive use, injectable contraceptive use, lifetime sexual partnership, parity of the patient, age at first pregnancy, year of diagnosis and interviewer's code. The global linear trend of each ordinal variable was assessed by adding the variables to the final model without the factor component. All tests of hypothesis were two- tailed and statistically, significant association was set at 95% confidence interval (P-value<0.05).

2.10.1.6 Multicollinearity.

Linear regression was run with the outcome and explanatory variables in each model, and the variance inflation factor (VIF) was determined for each variable. A VIF greater than 10 suggests collinearity. Also, before conducting the multivariable analysis, variables that are derivatives of the other were not both included in the same multivariable model to avoid multicollinearity.

2.11 Ethical considerations

Approval for the conduct of the study was obtained from the Human Research ethics committee ((Medical) of the University of Witwatersrand. (Clearance Certificate number: M141163 (Appendix I)). Permission was obtained from the respective record gate keepers of the datasets. The primary JCCCS study also has the approval of the ethics committee. Anonymised data were obtained, and they were kept in a password protected personal computer to ensure confidentiality of participants.

2.12 Future Opportunities for dissemination of the research findings

An executive summary of this study together with the full report will be presented to the relevant agency of the Department of health of South Africa so as to aid reviews, planning and targeted interventions and implementation of CC control programs in South Africa.

Further, writings in plain language on the key findings of this report will be produced to aid social marketing of the prevention of CC in South Africa and elsewhere.

Manuscripts to be submitted to relevant peer reviewed scientific journals and conference abstracts are already being developed from the major themes of this report to further disseminate the results of this research to the relevant scientific community, to aid public health interventions and implementation of our findings.

3 CHAPTER THREE

RESULTS

This chapter describes the socio-demographic characteristics of the patients who had or died from CC in South Africa between 1994 and 2012. Temporal trends in the incidence, mortality, 5-year relative survival rate of CC by population group, age group, histological type and province was also described. Finally, unconditional multivariable logistic regression of the three case-control sub-studies on the risk factors of CC among Black women was also presented.

3.1 Objective One: Trends of Cervical Cancer Incidence in South Africa (1994-2009)

3.1.1 Demographic and histological distribution

Over the 16 year study period (1994-2009), the overall number of cases was 75,099, and the average annual number of CC cases as reported to NCR was 4,694 cases per annum. About four-fifths of the CC cases occurred in Black women, and the least number of cases occurred in Indians/Asians. The peak age was 40-49 years (N= 18,717 (24.9%), closely followed by 50-59 years (N=17,264 (23.0%) (Table 3.1). The mean age at CC diagnosis was 52.3 (±13.7) years, and almost half (43.1%) of the cases were of reproductive age (15-49 years). About 4.2% of the CC cases had missing data for age and population group respectively. Squamous cell carcinoma (79.9%) was the most common histological type of CC, and the majority of CC (90%) cases were diagnosed in the public sector laboratories.

Table 3. 1: Demographic and histological characteristics of cases (1994-2009) and deaths (2004-2012) from cervical cancer in South Africa

Characteristics	**Cervical cancer cases, N= 75,099 N, (%)**	**Cervical cancer deaths, N=25,101 N, (%)**
Population Group		
Blacks	59,333 (79.0)	17,422 (69.4)
Coloureds	5,548 (7.4)	1,771 (7.1)
Whites	6,062 (8.1)	724 (2.9)
Indians/ Asians	1,016 (1.4)	218 (0.9)
Missing	3,140 (4.2)	4,966 (19.8)
Age (mean±SD)	52.3 (±13.7)	56.14 (±14.7)
<20	87 (0.1)	14 (0.1)
20-29	2,136 (2.8)	515 (2.1)
30-39	11,442 (15.2)	2,775 (11.1)
40-49	18,717 (24.9)	5,647 (22.5)
50-59	17,264 (23.0)	6,117 (24.4)

Table 3.1 continued

Characteristics	**Cervical cancer cases, N= 75,099 N, (%)**	**Cervical cancer deaths, N=25,101 N, (%)**
60-69	13,546 (18.0)	4,936 (19.7)
70-79	6,677 (8.9)	3,492 (13.9)
80 & above	2,049 (2.7)	1,565 (6.2)
Missing	3,181 (4.2)	40 (0.2)
Histologic types		
SCC	60,053 (79.9)	-
ADC	7,300 (9.7)	-
Others	7,746 ()10.3	-
Cervical cancer site		-
Endocervix	1,611 (2.2)	-
Exocervix	238 (0.3)	-
Overlapping	121 (0.2)	-
Cervix Uteri	73,129 (97.4)	-
Type of laboratory		
Government	67,564 (90.0)	-
Private	7,535 (10.0)	-
Marital status		
Never married	-	9,088 (36.2)
Married	-	5,153 (20.5)
Widowed	-	1,954 (7.8)
Divorced	-	2,349 (9.4)
Missing	-	6,557 (26.1)
Smoking status		
Yes	-	1,771 (7.1)
No	-	9,661 (38.5)
Missing	-	13,669 (54.5)
Highest Education		
No education	-	3,175 (12.7)
Primary school	-	4,406 (17.6)
High school	-	3,926 (15.6)
Tertiary	-	219 (0.9)
Missing	-	13,375 (53.3)
Province of residence		
Western Cape	-	1,916 (7.6)
Eastern Cape	-	2,988 (11.9)
Northern Cape	-	787 (3.1)
Free State	-	2,038 (8.1)
KwaZulu-Natal	-	4,387 (17.5)
North West	-	1,606 (6.4)
Gauteng	-	4,033 (16.1)
Mpumalanga	-	2,265 (9.0)
Limpopo	-	2,606 (10.4)
Others	-	2,475 (9.9)
Health Institution where Deaths Occurred		
Hospital	-	15,652 (62.4)
Home	-	5,496 (21.9)
Nursing home	-	453 (1.8)
Dead on arrival	-	371 (1.5)
Emergency room/Outpatient	-	326 (1.3)
Other	-	345 (1.4)
Missing	-	2,458 (9.8)

SD: Standard deviation

Further, the proportion of CC cases as reported by private laboratories ranged between 7.9% in 1995 and 13.1% in 2003 and was between 9-10% from 2004 to 2008 (Table not shown).

3.1.2 Trends in numbers of cervical cancer cases by population group, 1994-2009

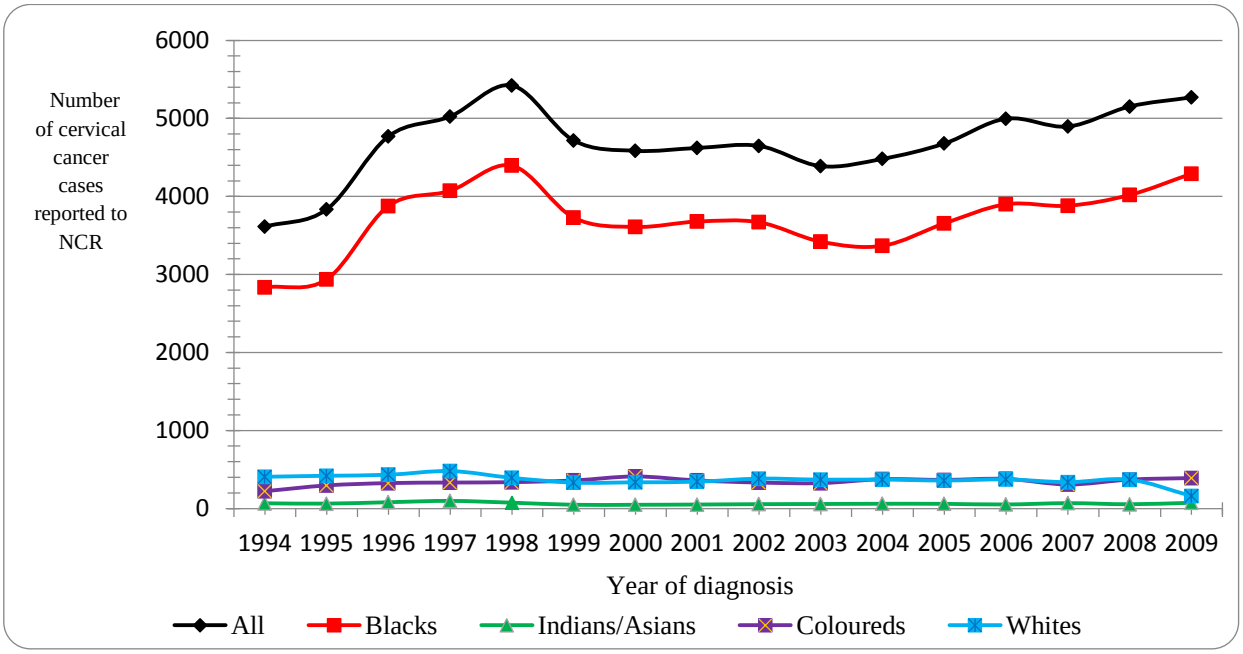

Figure 3. 1: Number of cervical cancer cases by population groups in South Africa as reported to NCR (1994-2009)

The numbers of CC cases reported to the NCR (all population groups) peaked in 1998 at 5,422 cases (Table 3.2). Thus, the average annual decline of CC cases was highest among the Indians/Asians (6.0 cervical cancer cases per million per annum, AAPC= -4.1% (95% CI:-4.4 - -3.9)) followed by Blacks (2.6 cases per million per annum, AAPC= -1.0%, 95%CI: -1.04 - -1.01), Coloureds (2.6 cases per million per annum, AAPC= -1.6%, 95% CI: -1.7 - -1.5) and Whites (2.1 cases per million, AAPC= -1.5%, 95% CI: -1.6 - -1.50)) (Figure 3.2).

3.1.3 Overall crude and age-standardised incidence rate and by population group, 1994-2009

The overall (all population group) ASIR over the 16 - year period decreased significantly by 0.9% annually (AAPC= -0.9%, 95%CI: -0.91 - -0.88). However, Figure 3.2 below, showed that there was a sharp increase in overall rates of about 7.6% per annum from 1994 to 1998 (from 22.1 to 29.2 per 100,000 women; AAPC = 7.6%, 95%CI: 7.60 - 7.62) and a subsequent decline in rates of about 8.5% per annum till 2001 (From 29.2 to 22.4 per

100,000; AAPC = -8.5% ; 95%CI: -8.53 - -8.45). Afterwards, there was a slow increase in CC rates at about 0.9% per annum from 2001 to 2009 (from 22.4 to 23.3 per 100,000; AAPC= 0.9%, 95%CI: 0.93 - 0.95). The trend relationship of the annual ASIR between 2001 and 2009 is given by:

ln (ASIR) = 0.009(calendar year) - 3.0. Thus, the ASIR is expected to be 23.0 and 26.3 per 100,000 women in 2015 and 2030 respectively (assuming situation remains the same). The annual crude incidence rate (CIR) was higher and had similar pattern as the annual ASIR throughout the study period as shown in Table 3.2

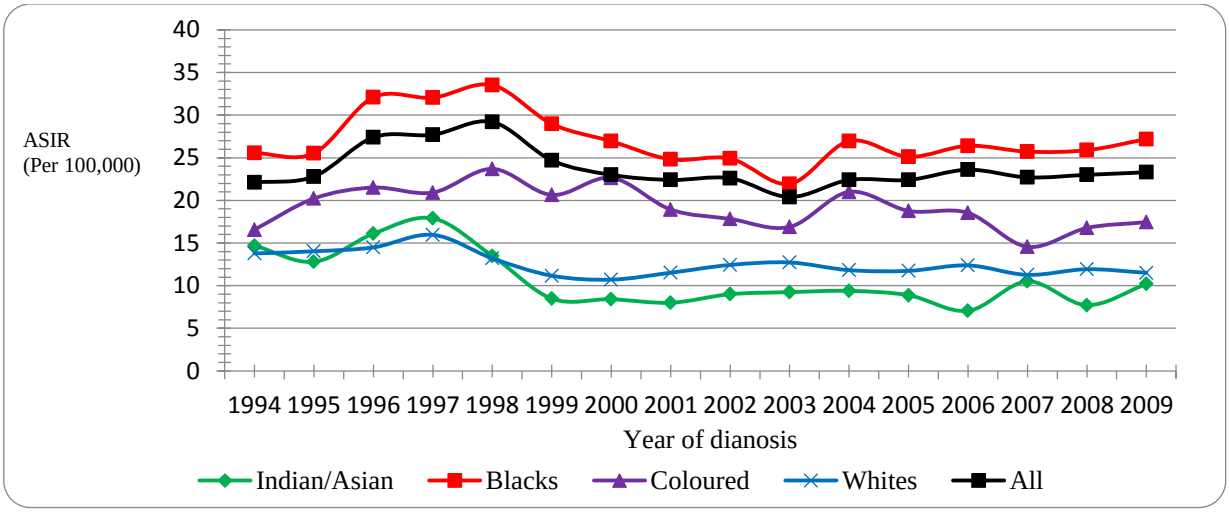

Figure 3. 2: Annual age-standardised incidence rates (ASIR) of cervical cancer by population group in South Africa (1994 to 2009).

In 2009, the Blacks had the highest ASIR of 27.2 per 100,000 women and this was about 1.6, 2.4 and 2.7 fold higher than in Coloureds (17.5/100,000 women), Whites (11.5/100,000 women) and Indians/Asians (10.2/100,000 women) respectively. Generally, the incidence rate increased from 1994 to 1997 and then dropped from 1997 to 2001 in all the population groups. However, from 2001 to 2009, there was an increase in CC incidence in the Blacks (AAPC= 1.3%, 95% CI: 1.28 - 1.31) and Indians/Asians (AAPC= 1.1%, 95% CI: 0.77 - 1.42) but Coloureds had reduced rates (AAPC= -1.5%, 95% CI: -1.57 - -1.41) while Whites (AAPC= -0.55%, 95% CI: -0.60 - 0.50) had slightly decreased rates (Figure 3.3)

Table 3. 2: Annual crude and age-standardised incidence and mortality rates of cervical cancer in South Africa (1994-2012)

Year	Mid-year population of women[a]	Cases (%)	CIR[b]	ASIR[c]	Death (%)	CMR[d]	[e]ASMR
1994	13342	3,613 (4.8)	27.1	22.1	-	-	-
1995	13749	3,834 (5.1)	27.9	22.8	-	-	-
1996	14155	4,770 (6.4)	33.7	27.4		-	-
1997	14562	5,025 (6.7)	34.5	27.7	-	-	-
1998	14969	5,422 (7.2)	36.2	29.2	-	-	-
1999	15375	4,717 (6.3)	30.7	24.7	-	-	-
2000	15782	4,585 (6.1)	29.1	23.0	-	-	-
2001	16189	4,621 (6.2)	28.5	22.4	-	-	-
2002	16412	4,648 (6.2)	28.3	22.6	-	-	-
2003	17002	4,388 (5.8)	25.8	20.4	-	-	-
2004	16596	4,482 (6.0)	27.0	22.4	2,576(10.3)	15.5	13.9
2005	16249	4,678 (6.2)	28.8	22.4	2,707 (10.8)	16.7	13.7
2006	16477	4,997 (6.7)	30.3	23.6	2,728 (10.9)	16.6	13.5
2007	16703	4,896 (8.5)	29.3	22.7	2,599 (10.4)	15.6	12.6
2008	17497	5,153 (6.9)	29.5	23.0	2,648 (10.6)	15.1	12.5
2009	17751	5,270 (7.0)	29.7	23.3	2,900 (11.6)	16.3	13.3
2010	17965	-	-	-	2,869 (11.4)	16.0	13.2
2011	18229	-	-	-	3,008 (12.0)	16.5	13.1
2012	18455	-	-	-	3,066 (12.2)	16.6	13.1
Total /overall		75,099	24.4		25,101	16.1	

[a] Mid-year population of women (≥15 years) per thousand women. [d]CMR: Crude mortality rate per100, 000 women. [e]ASMR: Age-standardized mortality rates per100,000 women. [b]CIR: Crude Incidence Rate per100, 000 women. [c]ASIR: Age-standardized Incidence Rates per100,000 women.

3.1.4 Trends in age-specific incidence rates and by population group, 1994-2009

Between 2000 and 2009, women who were 75 years or older had the highest increase in average incidence rates (AAPC= 6.8%, P-value < 0.001). Also, women between 25 and 49 years had increased incidence rates (AAPC range: 1.1% to 3.1%, p-value<0.001). In contrast, there was a decrease in incidence among teenagers (15-19 years) (AAPC = - 12.3%, P-value<0.001) and women aged 50-64years (AAPC range: -1.04% to - 3.0%, P-value <0.001). But the incidence rates were relatively stable among women aged 20-24 years (AAPC = 0.02%, P-value <0.001), 65-69 years (AAPC = -0.4%, P-value<0.001) and 70-74 years (AAPC = 0.3%, P-value<0.001).

Considering the cumulative age-specific incidence rates over the 16 year period (1994-2009), by population group as shown in Figure 3.4 below, the rates increased with increasing age in all population groups but the Whites had a slight steady decline in rates from 40 years (30.2/1000 women) to 74 years (26.5/100,000 women) and also had the lowest rates from 55 years. In contrast, the Black population had the highest rates from 30 years. However, the Indians/Asians had the lowest rates from 15 -54 years. The Coloured population had a similar pattern as the Blacks but had lower rates in all the age groups. The incidence rates sharply declined among the elderly (beyond 65 years) in all population groups.

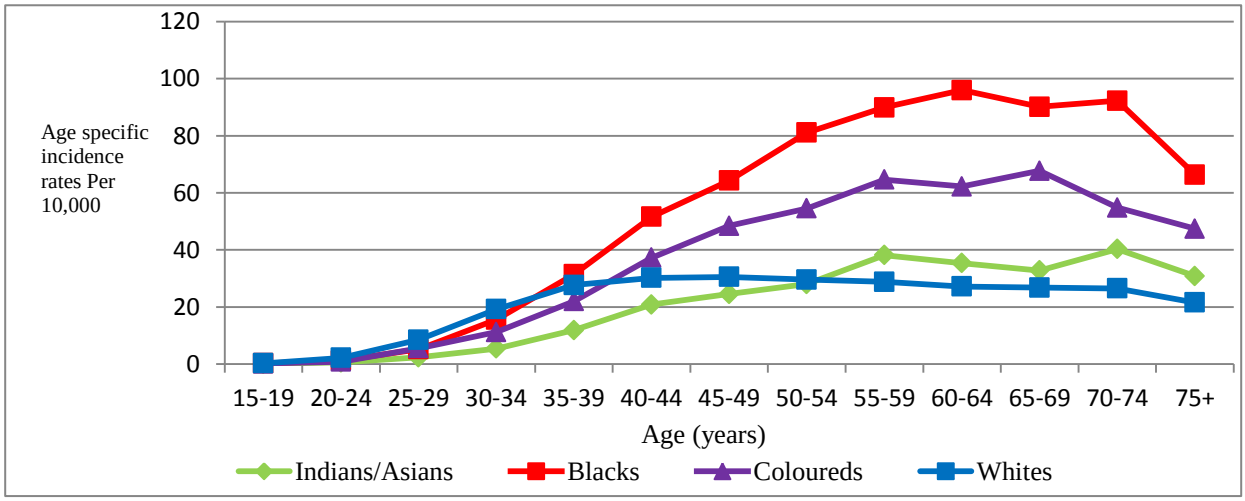

Figure 3. 3: Age-specific incidence rate of cervical cancer by population group in South Africa (1994-2009)

3.1.5 Incidence of major histological types of cervical cancer

The ASIR of SCC was 16.2/100,000 in 1994 and increased by 1.4% annually between 2000 (17.6/100,000) and 2009 (19.1/100,000), (AAPC=1.4% , P-value<0.001). However, the ASIR of ADC was relatively low during the study period (between 2.0 and 2.6 per 100,000 women and was about one-eighth of SCC rates), and was stable between 2000 and 2009 (AAPC= -0.3%, P-value<0.001) (Figure 3.4)

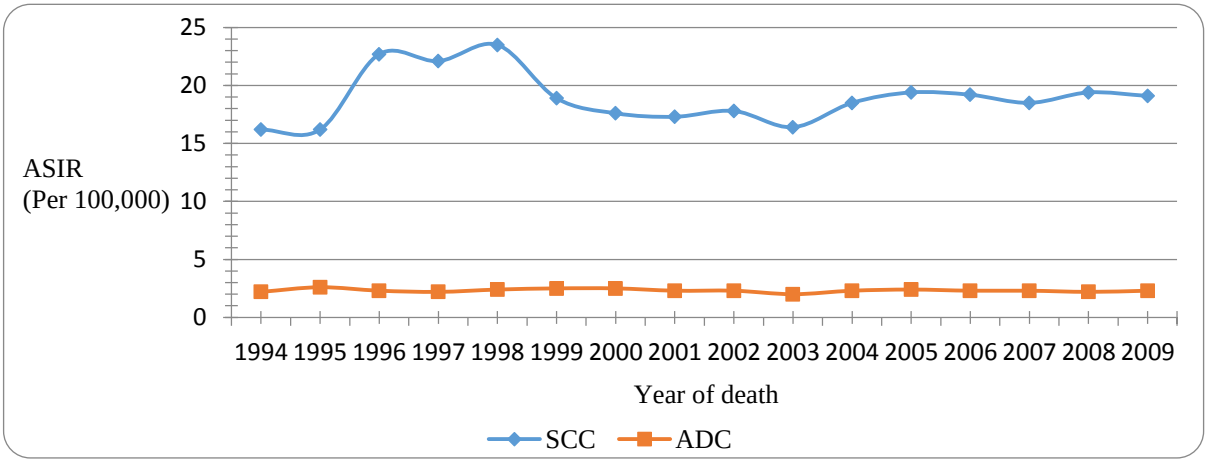

Figure 3. 4: Trends in the annual age standardised incidence rates of the major histological types of cervical cancer in South Africa (1994-2009).

3.2 Objective Two: Trends of cervical cancer mortality in South Africa (2004-2012)

3.2.1 Socio-demographic characteristics of deaths from cervical cancer

Over the 9 year study period (2004-2012), the total number of deaths from CC was 25,101, and the average annual deaths from CC were 2,789 per annum. The majority (69.4%) of deaths occurred in Blacks, and they had the highest annual number of CC mortalities throughout the study period (2004-2012) as shown in Figure 3.6 below. The peak age at death was 50-59 years (N=6,117, (24.4%) and closely followed by 40-49 years (N= 5,647 (22.5%) (Table 3.1). The mean age at death from CC was 56.1(±14.7) years, and about one-third (35.7%) of CC mortalities occurred in women of the reproductive age (15 - 49 years). Most of the deaths occurred in a hospital (15,625/25101, 62.4%) but more than one-fifth of the mortalities also occurred at home (5,496 /25101deaths; 21.9%). The smoking status (54.5%) and educational attainment (53.3%) of more than half of the fatalities were not ascertained (Table 3.1). However, complete case analysis showed that 15.8% (17771/11433)

were smokers while the majority (about 64.7% (7581/11726) had less than nine years of education.

3.2.2 Trends in numbers of deaths from CC by population group, 2004-2012

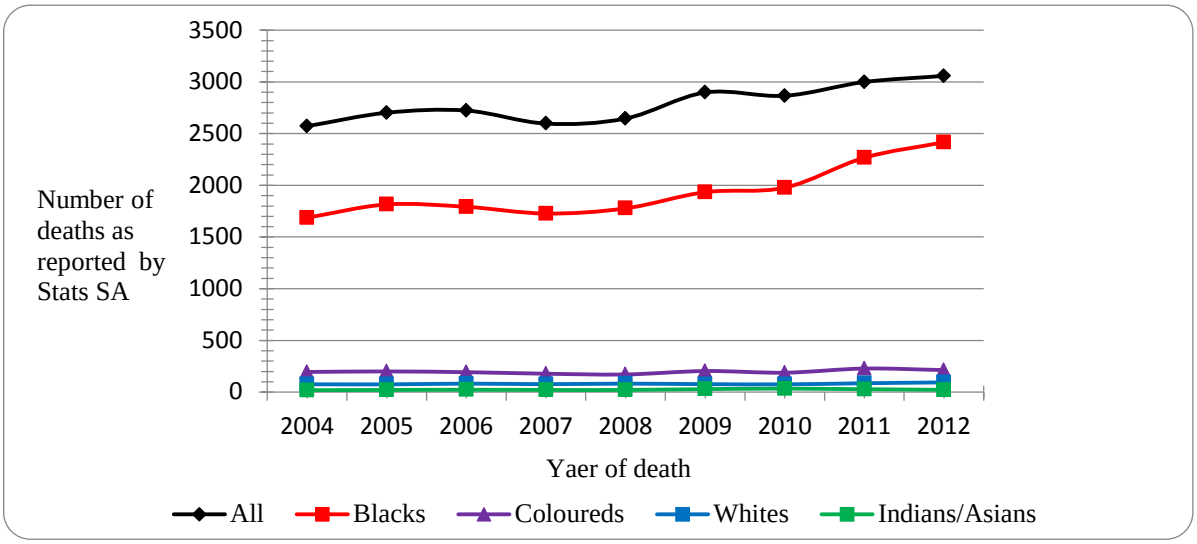

Figure 3. 5: Number of cervical cancer deaths by population groups in South Africa as reported by Stats SA (2004-2012).

The numbers of deaths from CC as reported to the Stats SA (all population groups) showed an upward trend from 2004 (2,572) to 2012 (3,058). However, on the average, there was a slight annual increase in mortality of 0.2 deaths (AAPC=1.1%, 95% CI: 1.3 - 1.8), 3 deaths (AAPC=1.4%, 95% CI: 1.4 - 1.5) and 19 deaths (AAPC = 1.5%, 95% CI: 1.4 - 1.7) per million women per annum among Indians/Asians, Whites and Blacks respectively. But there was a decline of 36 deaths per million women per annum (AAPC= -2.9%, 95%CI: -2.7 - -3.0) among Coloureds (Figure 3.5)

3.2.3 Overall crude and age-standardised mortality rate and by population group, 2004-2012

The overall (all population) ASMR over the 9 – year study period slightly decreased by 0.6% per annum from 2004 (13.9 per 100,000) to 2012 (13.1 per 100,000), (AAPC = -0.6% 95% CI: -0.60 - -0.58) (Figure 3.6, Table 3.2). However, Figure 3.7 shows two phases of the mortality trends. There was an initial decline in overall mortality rates of about 3.0% per annum from 2004 to 2008 (from 13.9 to 12.5 per 100,000 women; AAPC = -3.0%, 95% CI:

-3.04 – -3.55) and a subsequent increased rates of 0.8% per annum (AAPC = 0.8% ; 95% CI: 0.76 - 0.81) from 2008 to 2012 (from 12.5 to 13.1 per 100,000 women). The trend relationship of the annual ASMR between 2008 and 2012 is given by:

ln (ASMR) = 0.0078 (calendar year) + 2.5. Thus, the ASMR is expected to be 13.0 and 14.6 per 100,000 women in 2015 and 2030 respectively (assuming situation remains the same). When we compared the overall trends in incidence and mortality from Figure 3.2 and Figure 3.6, the decline in mortality from 2004 appears to lag and mirror the decline in incidence from 1998. Similarly, the apparent increase in mortality from 2008 appears to lag and mirror the increase in incidence from 2001.

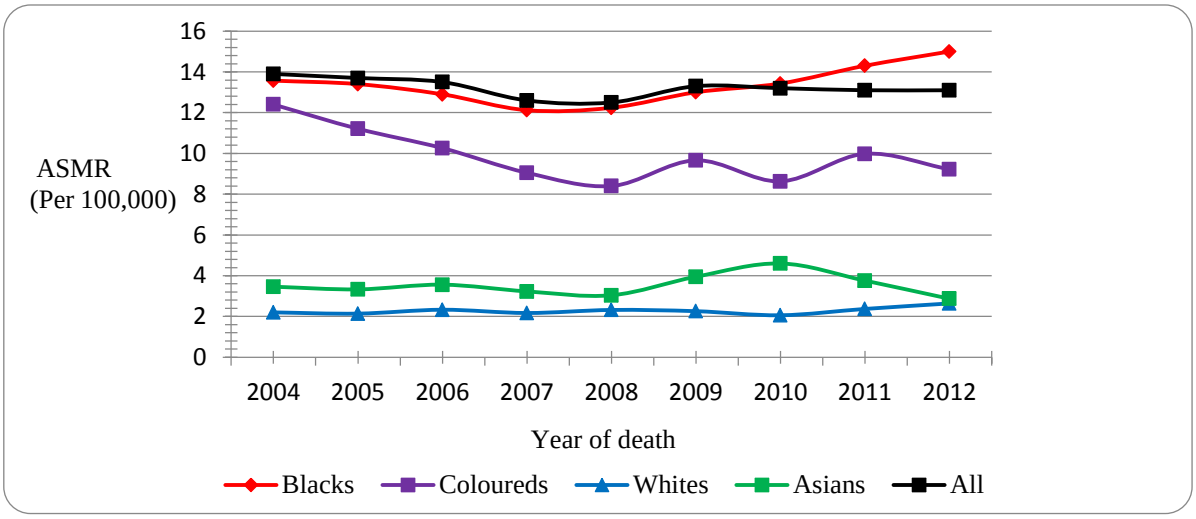

Figure 3. 6: Annual age standardised mortality rate of cervical cancer by population group in South Africa (1994-2009).

Also, the annual crude mortality rate (CMR) was 15.5 and 16.6 per 100,000 women in 2004 and 2012 respectively, and these rates were higher, but of similar pattern as the annual ASMR throughout the study period (2004 - 2012) as shown in Table 3.2

In 2012, the ASMR in Blacks (15.0 /100,000) was about 1.6, 5.2 and 5.8 fold higher than in Coloureds (9.2/100,000), Indians/Asians (2.9/100,000) and Whites (2.6/100,000) respectively. Between 2004 and 2012, there was an average annual increase in ASMR among the Indians/Asians (AAPC=1.1%, 95% CI: 0.3-1.8), Whites (AAPC=1.4%, 95% CI: 1.4 - 1.5) and Blacks (AAPC = 1.5%, 95% CI: 1.4 - 1.7), but Coloureds had reduced mortality rates that was about two fold the incremental rates in each of the other population groups (AAPC= -2.9%, 95% CI: -2.7 - -3.0) (Figure 3.6).

3.2.4 Trends in age-specific mortality rates of cervical cancer and by population group in South Africa (2004-2012)

Women in the younger age group of 25-29 years (AAPC=+4.1%, P-value <0.001) and 30-34 years (AAPC=+6.3%, P-value<0.001) had the highest average annual increase in mortality rates between 2004 and 2012 while women in the age range 35-49 years and those who were 60 years and older had negligible mortality increase: 35-39years (AAPC = 0.9%, P-value <0.001), 40-44 years (AAPC= 0.7%, P-value <0.001), 45-49 years (AAPC= 0.7%, P-value<0.001), 65-69 (AAPC= 0.6%, P-value<0.001), 70-74 (AAPC=0.7%, P-value<0.001), 75 and above (AAPC= 0.7%, P-value<0.001). There was a decline in the annual mortality rates among women in the age groups 20-24 (AAPC=-4.5%. P-value<0.001), 50-54 (AAPC=-1.0%, P-value <0.001), 55-59 (AAPC=-1.5%, P-value<0.001) and 60-64 (AAPC = -1.5%, P-value<0.001). Women between the ages of 15 and 19 years had increased rates that was not statistically significant (AAPC=+1.2%, P-value =0.8).

Considering the cumulative age-specific mortality rate of CC over the 9 year duration by population group as shown in Figure 3.8, the mortality rates increased with increasing age in all population groups. There was a steep rise in mortality rates from 30 years among all the population groups, and the rates were lowest in Whites and highest in Blacks. Coloureds had slightly lower and similar pattern of rates as the Blacks while Indians/Asians had slightly higher and similar rate as Whites. The rates in Whites largely plateaued from 40 to 69 years. There was a steep rise in mortality rates among the elderly in all population groups except in the Indians/Asians (Figure 3.7).

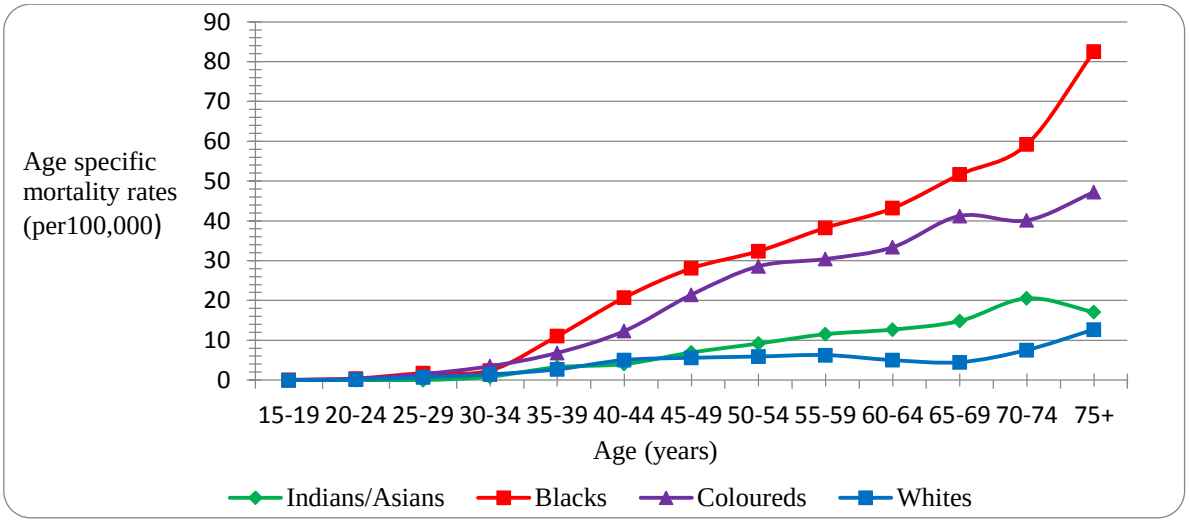

Figure 3. 7: Age-specific mortality rate of cervical cancer by population groups in South Africa (2004-2012).

3.2.5 Temporal trends in cervical cancer mortality in South Africa by province of residence (2004-2012)

In 2012, Mpumalanga (MP) (ASMR=19.8/100,000 women), North West (NW) (ASMR=18.5/100,000 women) and Northern Cape (NC) (ASMR= 18.0/100,000 women) had the highest tertile of provincial ASMR above 16/100,000 while Free State (FS) (ASMR = 15.9/100,000 women), Limpopo (LIM) (ASMR=14.8/100,000 women) and KwaZulu-Natal (KZN) (ASMR=14.5/100,000 women) had intermediate provincial mortality rates (middle provincial ASMR tertile) between 10 and 16 per 100,000. In contrast, Eastern Cape (EC) (8.9/100,000 women), Gauteng (GAU) (ASMR=9.7/100,000 women) and Western Cape (WC) (ASMR= 9.8/100,000 women) had the lowest provincial mortality rates below 10 mortalities per 100,000 women (lowest provincial ASMR tertile).

Neighbouring provinces had similar mortality rates as shown in Figure 3.8. Also, Figure 3.8 showed that the provinces with the highest mortality rates of more than 16/100,000 had international boundaries (MP, NW, NC). Considering provincial trends for the period 2004 to 2012, the highest increase in the average annual mortality rates occurred in NW province (from 8.6 to 18.5 per 100,000; AAPC= 8.3%, 95% CI: 8.1 - 8.5) while the greatest decline occurred at NC (from 23.5 to 18.0 per 100,000; AAPC= -16.6%, CI: 18.6 - 14.6) (See inset in Figure 3.8 and Appendix III).

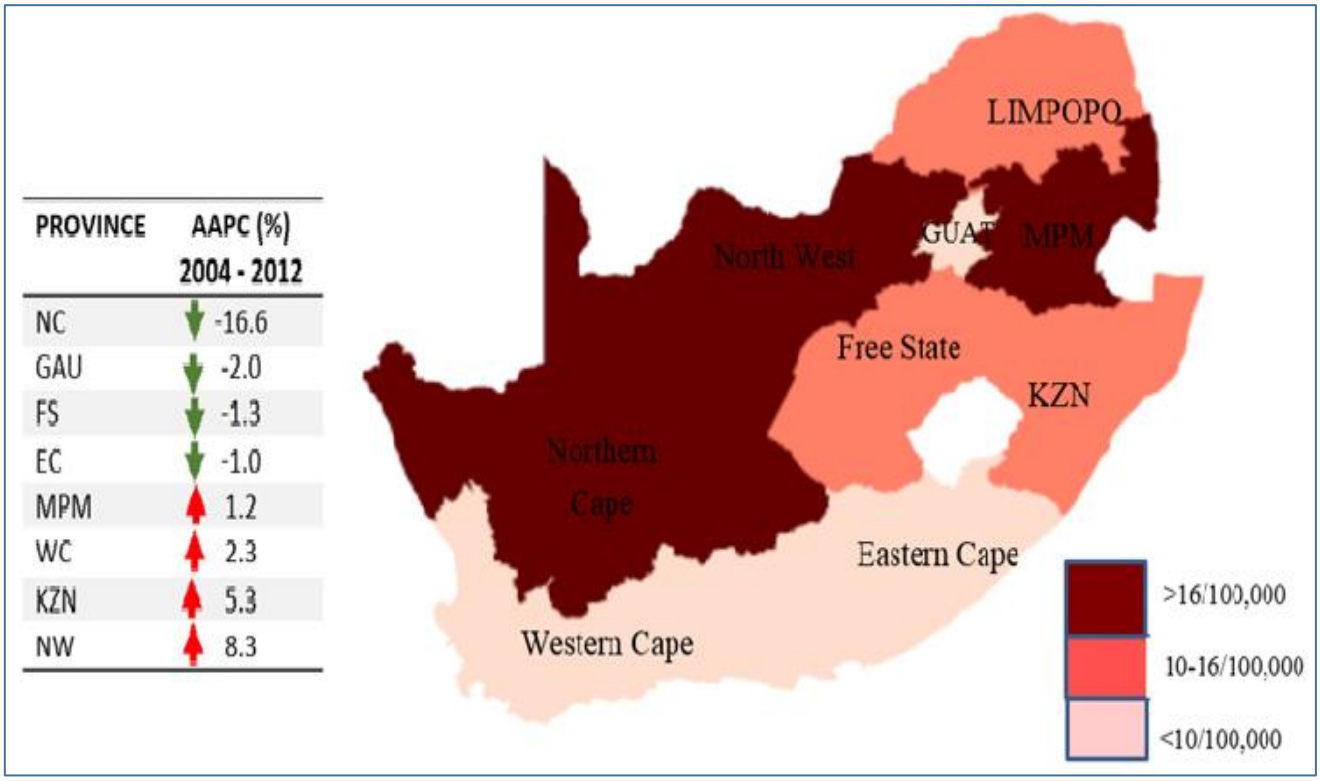

Figure 3. 8: Geographical distribution of age-standardised mortality rates (ASMR) of cervical cancer by province of residence in South Africa (2012) (Inset: Provincial trends in mortality rates (AAPC) between 2004 and 2012)

3.3 Objective Three: 5-year relative survival rates of cervical cancer in South Africa (2004-2009)

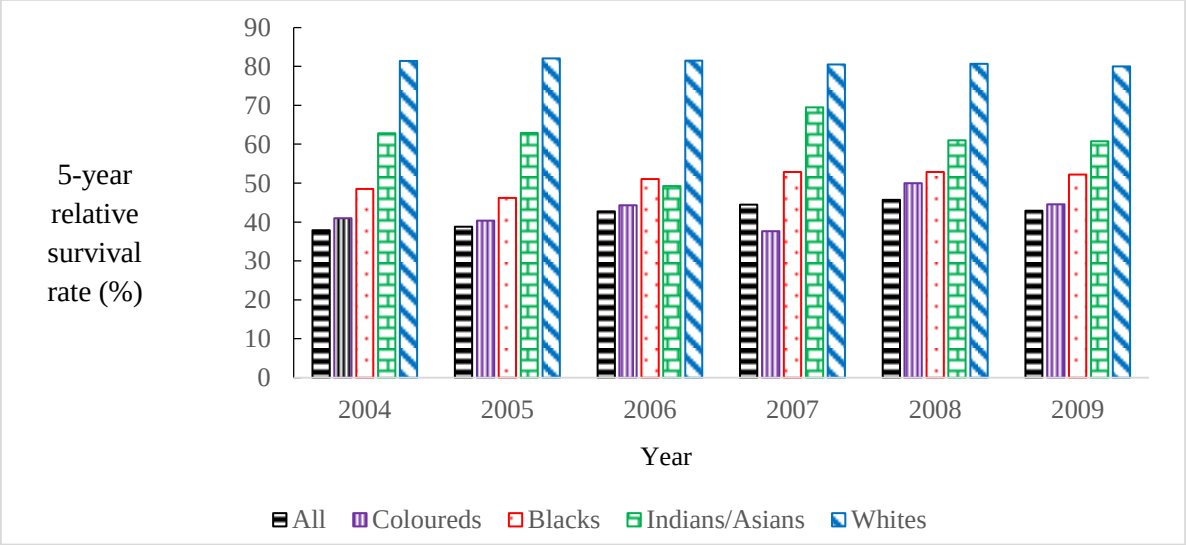

Figure 3. 9: Overall annual 5-year relative survival rates of cervical cancer and by population group in South Africa (2004-2009)

The overall 5-year relative survival rate (1-MI: IR) of CC in South Africa was poor (37.9 - 45.7%) between 2004 and 2009. Although, the Indians/Asians had a sporadic low survival rate of 49.3% in 2006, nonetheless Whites (80.0 – 82.1%) and Indians/Asians (60.8 - 69.5%) had relatively high 5-year relative survival rates during the period of study. However, the survival rates in Coloureds (37.7 - 50.0%) and Blacks (48.5 - 52.2%) were relatively low (Figure 3.9). There was an overall increase in 5-year relative survival rate of 13.2% between 2004 and 2009. Coloureds had the highest gain in the survival rate of 8.8% followed by Blacks (7.6%). There was a relatively minimal decline in survival rate among Indians/Asians (-3.2%) and Whites (-1.7%).

3.4 Objective Four: Cervical cancer risk factors in Black South Africans (JCCCS)

3.4.1 General characteristics of the Black participants of the JCCCS

In all, 10,562 Black female participants were recruited to the JCCCS between 1995 and 2010 (Figure 2.2). Fourteen (14) participants were excluded because they had unspecified cancer sites giving us a total of 10,548 participants for further analysis. Of these female participants, about one-third (3,546; 33.6%) had CC (Figure 2.2, Table 3.3). The prevalence of HIV and smoking was slightly higher among the CC participants as compared to other female cancer participants (For HIV: 22.9% vs 21.0%, P-value=0.002; For smoking: 21.1% vs 18.9%, P-value=0.001). The percentage of missing values among the variables was generally less than 2.0% except for HIV status (7.0%) (Table 3.4). Of the 7,322 female participants that were recruited from 2001 to 2010 after the introduction Pap smear history to the study, only about a quarter (23.5%, 1,723/7,322) ever had Pap smear before their cancer diagnosis, while virtually equal number (23.82%; 1,744/3) had diagnostic smears, data not shown.

Table 3. 3: Baseline socio-demographic characteristics of cervical cancer cases and other female cancer cases in the JCCCS (1995-2010).

Characteristics	**Other Female cancers N=7,002(%)**	**Cervical cancer N= 3,546(%)**	**Total N=10,548 (%)**	**Test statistics**	**P-value**
Age mean (±SD)	50.4±14.2	50.5±11.3	50.4(± 13.3)	-0.56[a]	0.57
<50	3,301(47.1)	1,702 (48.0)	5,003(47.4)	1.08[b]	0.58
≥ 50	3,697 (52.8)	1,843(52.0)	5,540(52.5)		
Missing data	4(0.06)	1(0.03)	5(0.05)		
15-19	37(0.5)	0(0.0)	37(0.4)	301.42[b]	<0.001*
20-24	180(2.6)	10(0.3)	190 (1.8)	-0.16[c]	0.87
25-29	326(4.7)	61(1.7)	387 (3.7)		
30-34	517(7.4)	195(5.5)	712 (6.8)		
35-39	621(8.9)	360(10.2)	981 (9.3)		
40-44	805(11.5)	505(14.2)	1,310(12.4)		
45-49	815(11.7)	571(16.1)	1,386(13.2)		
50-54	887(12.7)	575(16.2)	1,462(13.9)		
55-59	849(12.1)	500(14.1)	1,349(12.8)		
60-64	711(10.2)	320(9.0)	1,031 (9.8)		
65-69	586(8.4)	259(7.3)	845 (8.0)		
70-74	399(5.7)	136(3.8)	535 (5.1)		
75 and above	265 (3.8)	53(1.5)	318(3.0)		
Missing data	4(0.06)	1(0.03)	5(0.05)		
HIV status					
Negative	5,105(72.9)	2,421(68.3)	7,526(71.4)	38.29[a]	<0.001*
Positive	1,471(21.0)	813(22.9)	2,284(21.7)		
Missing data	426(6.1)	312(8.8)	738(7.0)		
Educational qualification					
No education	917(13.1)	737(20.8)	1,654(15.7)	239.08[b]	<0.001*
Primary school	2,211(31.6)	1,317(37.1)	3,528(33.5)	-14.8[c]	<0.001*
High school	3,562(50.9)	1,419(40.0)	4,981(47.2)		
Tertiary	286(4.1)	44(1.2)	330 (3.1)		
Missing data	26(0.4)	29(0.8)	55 (0.5)		
Type of residence Urban/Rural					
Urban	6,037(86.2)	2,751(77.6)	8,788(83.3)	129.62[b]	<0.001*
Rural	928(13.3)	776(21.9)	1,704(16.2)		
Missing data	37(0.5)	19(0.5)	56(0.5)		

Table 3.3 continued

Characteristics	Other Female cancers N=7,002(%)	Cervical cancer N= 3,546(%)	Total N=10,548 (%)	Test statistics	P-value
Tobacco Smoking					
Non-smokers	5,678(81.1)	2,799(78.9)	8,477(80.4)	12.65[b]	0.01*
Ex-smokers	505(7.2)	256(7.2)	761(7.2)	-2.79[c]	0.001*
Current light smoker (1-14g/day)	672(9.6)	417(11.8)	1,089(10.3)		
Current heavy smoker (>14g/day)	118(1.7)	56(1.6)	174 (1.7)		
Missing data	29(0.4)	18(0.5)	47(0.5)		
Snuff ever use					
Never	5,178(74.00)	2,449(69.1)	7,627(72.3)	90.09[b]	<0.001*
In the Past	920(13.1)	395(11.1)	1,315(12.5)	-6.5[c]	<0.001*
Current users	894(12.8)	698(19.7)	1,592(15.1)		
Missing data	10(0.1)	4(0.1)	14(0.1)		
Alcohol use					
Non drinkers	3788(54.1)	1,599(45.1)	5,387(51.1)	84.9[b]	<0.001*
Moderates drinkers	2,767 (39.5)	1,696 (47.8)	4,463(42.3)	8.01[c]	<0.001*
Heavy/binge drinkers	432(6.2)	231 (6.5)	663 (6.3)		
Missing data	15(0.2)	20 (0.6)	35(0.33)		
Marital status					
Single/Never Married	1,554(22.2)	661 (18.6)	2,215(21.0)	19.01[b]	0.001*
Married/Living together	3,017(43.1)	1,630(46.0)	4,647(44.1)		
Widowed	1,490(21.3)	768(21.7)	2,258(21.4)		
Separated	921(13.2)	478(13.5)	1,399(13.3)		
Missing	20 (0.3)	9 (0.3)	29 (0.3)		
Province of residence					
Gauteng	5,713(81.6)	2,432(68.6)	8,145 (77.2)	246.4[b]	<0.001*
Limpopo	273(3.9)	279(7.9)	552 (5.2)	14.5[c]	<0.001*
Mpumalanga	142 (2.0)	101(2.9)	243 (2.3)		
North West	361 (5.2)	349(9.8)	710 (6.7)		
Free State	103 (1.5)	76(2.1)	179 (1.7)		
Eastern Cape	91(1.3)	64 (1.8)	155 (1.5)		
Western Cape	8(0.1)	6(0.2)	14 (0.1)		
Northern Cape	12(0.2)	20(0.6)	32 (0.3)		
KwaZulu Natal	175 (2.5)	129 (3.6)	304 (2.9)		
Missing	124(1.8)	90(2.5)	214(2.0)		
Year of interview					
1995 – 2000	1,873(26.8)	1,353(38.2)	3,231(30.6)	168.6[b]	<0.001*
2001 – 2005	2,391(26.1)	939(18.3)	3,331(23.5)	-7.8[c]	<0.001*
2006 – 2010	3,301(47.1)	1,546(43.6)	4,847(46.0)		

[a] t-test score, [b] Pearson's Chi-square, [c] Chi-square for trend. * Statistically significant P-value at <0.05. SD: Standard deviation

3.4.2 Case-control study I: HIV as major risk factor of cervical cancer.

There were 3,546 CC cases and 1,362 appropriate controls for HIV as the major risk factor of CC.

Univariable analysis

HIV status, Age ≥50, injectable contraceptives and Pap smear screening status were some variables that were individually associated with CC in Black South Africans when HIV was considered as the major risk factor of CC (Table 3.4)

Multivariable analysis

After adjusting for confounding variables, the odds of CC among HIV-positive women was about 2.6 times the odds in HIV-negative women (AdjOR= 2.6, 95% CI: 2.12 - 3.24; P-value <0.001). Also, women who were 50 years or older were about 38% less likely to be diagnosed with CC as compared to women of the reproductive age (18-49 years) (AdjOR=0.62 95% CI: 0.53 - 0.73, P-value<0.001) (Table 3.4).

When the analysis was restricted to the pre-ART (1995-2003) and ART eras (2004-2010), the odds of CC among HIV positive women was found to increase from about two-fold (AdjOR =1.93, 95% CI: 1.32 - 2.82, P-value = 0.001) during the pre-ART era to about three-fold (AdjOR = 2.92, 95% CI: 2.25 - 3.79, P-value<0.001) during the ART era. The sub-analysis further revealed that there was a preponderance of diagnosing more CC cases in women older than 50 years in the ART era as compared to the pre-ART era. (For ART era: AdjOR of age ≥ 50 = 0.70, 95% CI: 0.56 - 0.89, P-value 0.004; for pre-ART era: AdjOR = 0.53, 95% CI: 0.42 - 0.68, P0 value < 0.001).

The likelihood of diagnosing CC among the female Black participants in the period of 2001 – 2004 and 2005 – 2010 were 57% and 40% less than the period between 1995 and 2000 (Ptrend < 0.001). Lower parity (Ptrend < 0.001), delayed age at first pregnancy (Ptrend < 0.001and higher educational attainment (Ptrend < 0.001) were protective of CC. Women who used injectable contraceptives beyond 5 years had 1.8 fold odds of developing CC as compared to women that never used injectable contraceptives. The odds reduced to 1.6 fold after the tenth year of use (which may be artefactual because of poor long-term recall) (Table 3.4). However, there was no association between oral contraceptive and CC in this study, and there was no interaction between HIV status and injectable contraceptive use.

Table 3. 4: Crude and adjusted odd ratios of the risk of cervical cancer when HIV is the major risk factor. (Case-control study I)

	Univariable analysis			Multivariable analysis		
Factor	**COR**	**95% CI**	**P-value**	**AdjOR**	**95% CI**	**P-value**
HIV status						
Negative	1.00	Ref	Ref	1.00	Ref	Ref
Positive	2.52	2.08 - 3.04	<0.001*	2.62	2.12 - 3.24	<0.001*
Missing Data	1.26	1.00 - 1.58	0.048	1.04	0.80 - 1.34	0.784
Age						
<50	1.00	Ref	Ref	1.00	Ref	Ref
≥ 50	0.65	0.57 - 0.74	<0.001*	0.62	0.53 - 0.73	< 0.001*
Missing Data	0.30	0.02 - 4.82	0.400	0.22	0.02 - 1.92	0.170
Smoking status						
Never	Ref	Ref	Ref	Ref	Ref	Ref
Past smokers	1.06	0.83 - 1.35	0.659	1.18	0.90 - 1.55	0.223
Current light smokers	1.56	1.25 - 1.95	<0.001*	1.97	1.53 - 2.52	< 0.001*
Current heavy smokers	2.54	1.25 - 5.15	0.010*	3.21	1.51 - 6.79	0.002*
Missing data	3.68	0.85 - 15.87	0.081	2.60	0.50 - 13.35	0.253
P-value for trend			*<0.001**			*<0.001**
Snuff ever use						
Never				Ref	Ref	Ref
Ex users	0.85	0.70 - 1.03	0.09	0.92	0.75 - 1.14	0.439
Current users	1.43	1.20 - 1.70	<0.001*	1.40	1.16 - 1.70	0.001*
Missing data	0.80	0.15 - 4.37	0.796	0.72	0.11 - 4.61	0.727
P-value for trend			*<0.001**			*0.002**
Educational qualification						
No education	Ref	Ref	Ref	Ref	Ref	Ref
Primary school	0.87	0.72 - 1.05	0.146	0.87	0.70 - 1.05	0.134
High school	0.65	0.55 - 0.78	<0.001*	0.67	0.54 - 0.82	< 0.001*
Tertiary	0.27	0.17 - 0.41	<0.001*	0.33	0.20 - 0.55	< 0.001*
Missing data	1.43	0.59 - 3.49	0.432	1.62	0.62 - 4.22	0.321
P-value for trend			*<0.001**			*<0.001**
Place of residence						
Urban	1.00	Ref	Ref	1.00	Ref	Ref
Rural	1.59	1.34 - 1.88	<0.001*	1.44	1.19 - 1.75	< 0.001*
Missing	1.99	0.68 - 5.87	0.212	1.99	0.61 - 6.49	0.255
Oral Contraceptives use						
Never	1.00	Ref	Ref			
yes, <5years	1.10	0.91 - 1.34	0.334			
yes≥5<10years	1.27	0.94 - 1.71	0.122			
yes≥10years	1.11	0.84 - 1.48	0.465			
Missing data	0.76	0.48 - 1.20	0.240			
Injectable Contraceptives use						
Never	1.00	Ref	Ref	1.00	Ref	Ref
yes, <5years	1.43	1.19 - 1.70	<0.001*	1.25	1.03 - 1.51	0.024*
yes≥5<10years	2.30	1.75 - 3.02	<0.001*	1.85	1.38 - 2.50	<0.001*
yes≥10years	1.93	1.51 - 2.46	<0.001*	1.62	1.22 - 2.13	0.001*
Missing Data	1.01	0.68 - 1.52	0.94	1.01	0.66 - 1.54	0.970
P-value for trend			*<0.001**			*<0.001**

Table 3.4 continued

	Univariable analysis			Multivariable analysis		
Factor	COR	95% CI	P-value	AdjOR	95% CI	P-value
Lifetime number of sexual partners						
0-1 partner	1.00	Ref	Ref	1.00	Ref	Ref
2-5 partners	1.58	1.32 - 1.88	<0.001	1.38	1.13 - 1.68	0.001*
5 and above	1.80	1.40 - 2.32	<0.001	1.56	1.18 - 2.06	0.002*
Missing data	0.70	0.49 – 1.00	0.05	0.76	0.51 - 1.13	0.175
P-value for trend			*<0.001**			*<0.001**
Marital status						
Single/Never Married				Ref	Ref	Ref
Married/Living together	1.31	1.10 - 1.55	0.002*	1.28	1.05 - 1.56	0.014*
Widowed	0.97	0.80 - 1.17	0.731	1.01	0.81 - 1.27	0.912
Separated	1.20	0.96 - 1.50	0.106	1.30	1.00 - 1.67	0.047*
Missing data	0.66	0.23 - 1.86	0.428	0.67	0.23 - 1.96	0.459
Age at first pregnancy						
≤16yrs	Ref	Ref	Ref	Ref	Ref	Ref
>16<21yrs	0.74	0.59 - 0.93	0.012*	0.86	0.67 - 1.10	0.243
21&above	0.58	0.46 - 0.73	<0.001*	0.72	0.56 - 0.92	0.009*
Missing data	0.24	0.18 - 0.32	<0.001	0.63	0.38 - 1.03	0.066
P-value for trend			*<0.001**			*<0.001**
Parity						
0	Ref	Ref	Ref	Ref	Ref	Ref
1-2	4.48	3.29 - 6.10	<0.001*	3.02	1.75 - 5.21	<0.001*
3-5	5.69	4.18 - 7.75	<0.001*	3.95	2.28 - 6.85	<0.001*
6&above	6.26	4.58 - 8.55	<0.001*	5.30	3.04 - 9.23	<0.001*
Missing	4.25	2.53 - 7.13	<0.001	2.84	1.60 - 5.06	<0.001*
P-value for trend			*<0.001**			*<0.001**
Year of interview						
1995 – 2000	Ref	Ref	Ref	Ref	Ref	Ref
2001 – 2005	0.47	0.40 - 0.56	<0.001*	0.43	0.35 - 0.52	<0.001*
2006 – 2010	0.71	0.61 - 0.82	<0.001*	0.60	0.51 - 0.72	<0.001*
P-value for trend			*<0.001**			*<0.001**
Pap smear screen before cancer diagnosis						
Never	Ref	Ref	Ref			
Ever	0.53	0.44 - 0.64	<0.001*			
Missing	0.86	0.75 - 0.99	0.030			

Hosmer-Lemeshow Chi-square (8) = 13.14, P-value = 0.1071. Multivariable Model built with: HIV, Age ≥50, Place of residence (rural/urban), injectable contraceptives, parity, age at first pregnancy, marital status, tobacco smoking, snuff use, year of diagnosis and educational attainment. COR: crude odds ratio. Adj OR: Adjusted odds ratio.

The sensitivity analysis of including Pap Smear in the model that was restricted to ART era (2004 – 2010), which was four years after the commencement of population-based screening in 2000, did not alter the odds of diagnosing CC in HIV-positive patients (AdjOR for HIV: 3.0, 95% CI: 2.30 - 3.91, P-value <0.001).

3.4.3 Case-control study II: Tobacco smoking and alcohol as major risk factors of cervical cancer

There were 3,546 CC cases and 1,327 appropriate controls for smoking as the major risk factor of CC.

Univariable analysis

Tobacco smoking and age ≥50years, snuff use, oral and injectable contraceptive usage were individually associated with CC in Black South African women when considering tobacco smoking and alcohol abuse as major risk factor of CC. Also, moderate alcohol drinkers had 46% increased odds of CC as compared to non-drinkers. (COR = 1.46, 95% CI: 1.28 – 1.67, P-value < 0.001) (Table 3.5).

Multivariable analysis

After adjusting for confounding variables, the odds of CC increased with increasing amount of tobacco smoked as compared to non-smokers (Ptrend <0.001). Furthermore, current heavy smokers had about two-fold odds of CC as compared to non-smokers (AdjOR=2.2, 95% CI: 1.14 - 4.17, P-value=0.018). Also, there was no statistically significant difference in risk of CC among women that stopped smoking at least 5 years earlier and non-smokers (AdjOR=1.34, 95% CI: 0.90 - 1.62, P-value=0.219). The current users of snuff had 30% increased likelihood of developing CC as compared to women that never used snuff (AdjOR =1.3 CI: 1.06 - 1.58; P-value=0.01) and there was no statistically significant difference in risk between former users of snuff and never users.(P-value = 0.441). Alcohol did not retain its univariable association with CC after correcting for confounders. The odds of CC increased with prolonged use of oral and injectable contraceptives beyond 5 years (Ptrend < 0.001). There were similar protective associations between CC and educational attainment, parity, and age at first pregnancy as obtained from our case-control study I (HIV) above. However, HIV-positive status showed a protective relationship (which we believe is artefactual) with CC (AdjOR = 0.55 CI: 0.47 – 0.65, P-value < 0.001), but this model was primarily designed to evaluate smoking and alcohol as a major risk factor of CC.

Table 3. 5: Crude and adjusted odd ratios of the risk of cervical cancer when Tobacco smoking and alcohol use are the major risk factor (Case-control study II)

	[1]Univariable logistic regression analysis			[2]Multivariable regression analysis		
Factors	**COR**	**95% CI**	**P-value**	**Adj OR**	**95%CI**	**P-value**
Smoking status						
Never	1.00	Ref	Ref	1.00	Ref	Ref
Ex-smoker	1.24	0.96-1.60	0.107	1.20	0.90 - 1.62	0.219
Current light smoker (1-14g/day)	1.35	1.09 - 1.68	0.005*	1.71	1.35 - 2.17	< 0.001*
Current heavy smoker (>14g/day)	1.71	0.93 - 3.13	0.085	2.18	1.14 - 4.17	0.018*
Missing data	7.13	0.95 - 53.50	0.056	5.61	0.54 - 58.50	0.150
P-value for trend			*<0.001**			*<0.001**
Alcohol use						
Non-drinkers	1.00	Ref	Ref	1.00	Ref	Ref
Moderate drinkers	1.46	1.28 - 1.67	<0.001*	0.98	0.80 - 1.19	0.807
Heavy/binge drinkers	1.15	0.88 - 1.48	0.300	1.16	0.86 - 1.56	0.330
Missing data	2.23	0.76 - 6.56	0.142	1.54	0.44 - 5.41	0.503
P-value for trend			*<0.001**			
Age						
<50	1.00	Ref	Ref	1.00	Ref	Ref
≥ 50	1.48	1.30 -1.68	<0.001*	0.82	0.70 - 0.98	0.025*
Missing data	0.45	0.03 - 7.20	0.57	0.13	0.01 - 1.34	0.088
Snuff ever use						
Never	1.00	Ref	Ref	1.00	Ref	Ref
Ex users	1.08	0.89 - 1.33	0.440	1.09	0.87 - 1.36	0.441
Current users	1.49	1.25 - 1.78	<0.001*	1.30	1.06 - 1.58	0.010*
Missing data	0.54	0.12 - 2.41	0.423	0.42	0.07- 2.41	0.333
P-value for trend			*<0.001**			*0.019**
HIV status						
Negative	1.00	Ref	Ref	1.00	Ref	Ref
Positive	0.44	0.38 - 0.51	< 0.001	0.55	0.47 - 0.65	< 0.001*
Missing Data	0.99	0.78 - 1.27	0.963	1.03	0.79 - 1.35	0.824
Age at first pregnancy						
≤16yrs	1.00	Ref	Ref	1.00	Ref	Ref
>16<21yrs	0.88	0.70 - 1.09	0.240	0.89	0.71 - 1.13	0.338
21&above	0.79	0.63 - 0.99	0.038*	0.80	0.63 - 1.01	0.060
Missing data	0.26	0.19 - 0.34	< 0.001*	0.60	0.37 - 0.99	0.044
P-value for trend			*<0.001**			*0.033 **
Parity						
0	1.00	Ref	Ref	1.00	Ref	Ref
1-2	4.21	3.12 - 5.67	<0.001*	2.51	1.47 - 4.30	0.001*
3-5	8.07	5.95 - 10.95	< 0.001*	4.15	2.41 - 7.13	< 0.001*
6&above	9.76	7.15 - 13.33	< 0.001*	4.49	2.58 - 7.80	< 0.001*
Missing	4.94	2.95 - 8.26	< 0.001*	2.72	1.56 - 4.72	< 0.001*
P-value for trend			*<0.001**			*<0.001**
Oral Contraceptive use						
Never	1.00	Ref	Ref	1.00	Ref	Ref
yes, <5years	0.98	0.82 - 1.19	0.873	1.11	0.91 - 1.36	0.295
yes, 5-10years	1.45	1.05 - 1.99	0.022*	1.57	1.12 - 2.20	0.009*
yes, ≥10years	1.33	0.98 - 1.80	0.067	1.67	1.21 - 2.32	0.002*
Missing data	0.67	0.43 - 1.04	0.075	0.78	0.46 - 1.30	0.333
P-value for trend			*0.015**			<0.001*

Table 3.5 continued

	Univariable analysis			Multivariable analysis		
Factor	COR	95% CI	P-value	AdjOR	95% CI	P-value
Injectable contraceptives use						
Never	1.00	Ref	Ref	1.00	Ref	Ref
yes, <5years	0.87	0.73 - 1.02	0.089	0.99	0.83 - 1.20	0.955
yes, 5-10years	0.97	0.78 - 1.21	0.786	1.28	1.00 - 1.64	0.047*
yes,≥10years	1.30	1.03 - 1.64	0.025*	1.80	1.39 - 2.33	< 0.001*
Missing data	0.61	0.42 - 0.88	0.009	0.89	0.59 - 1.32	0.552
P-value for trend			*0.163*			<0.001*
Marital status						
Single/Never Married	1.00	Ref	Ref	1.00	Ref	Ref
Married/Living together	1.91	1.62 - 2.24	< 0.001*	1.47	1.23 - 1.77	< 0.001*
Widowed	1.80	1.49 - 2.18	< 0.001*	1.16	0.93 - 1.45	0.194
Separated	1.69	1.36 - 2.09	< 0.001*	1.39	1.10 - 1.77	0.006*
Missing data	0.76	0.28 - 2.06	0.593	0.44	0.15 - 1.30	0.138
Educational qualification						
No education	1.00	Ref	Ref	1.00	Ref	Ref
Primary school	0.84	0.69 - 1.03	0.096	0.88	0.71 - 1.10	0.269
High school	0.46	0.38 - 0.55	< 0.001*	0.64	0.51 - 0.80	< 0.001*
Tertiary	0.20	0.13 - 0.31	< 0.001*	0.46	0.29 - 0.74	0.001*
Missing data	6.85	0.93 - 50.62	0.059	8.19	1.06 - 63.47	0.044
P-value for trend			*<0.001**			*<0.001**
Type of residence Urban/Rural						
Urban	1.00	Ref	Ref	1.00	Ref	Ref
Rural	1.87	1.56 - 2.24	< 0.001*	1.49	1.22 - 1.82	< 0.001*
Missing data	1.13	0.47 - 2.70	0.780	1.02	0.32 - 3.21	0.977
Year of interview						
1995 – 2000	1.00	Ref	Ref	1.00	Ref	Ref
2001 – 2005	0.44	0.37 - 0.52	<0.001*	0.47	0.37 - 0.60	<0.001*
2006 – 2010	0.57	0.49 - 0.66	<0.001*	0.65	0.51 - 0.82	<0.001*
P-value for trend			*<0.001**			<0.001*
Ever had pap smear						
Never	1.00	Ref	Ref			
≥1	0.62	0.51 - 0.75	<0.001*			
Missing data	1.06	0.92 - 1.21	0.422			

Hosmer-Lemeshow chi2(8) = 7.66, P-value =0.47. Multivariable Model built with: HIV, Age ≥50, Place of residence (rural/urban), injectable contraceptives; oral contraceptive, time period of diagnosis, parity, age at first pregnancy, marital status, tobacco smoking, snuff use, alcohol use, educational attainment and year of diagnosis. COR: crude odds ratio. Adj OR: Adjusted odds ratio.

Interaction between smoking and hormonal contraceptive

When we introduced the interaction term between smoking status and injectable contraceptives, we found that the use of injectable contraceptive by smokers was protective of CC in them. Thus, while current light smokers who were on injectable contraceptives for less than 5 years had about 65% lesser chance (for current light smokers#injectable usage of <5 years, AdjOR = 0.35 CI: 0.20 – 0.60, P-value for interaction <0.001) of developing CC as

compared to women who never smoked nor accepted injectable contraceptive (the reference group), the current light smokers who used injectable contraceptives beyond five years did not have statistically significant difference in risk as compared to the reference group (for current light smokers# injectable usage of 5-10 years, AdjOR = 0.72, 95% CI: 0.30 – 1.73, P-value for interaction = 0.46 and for current light smokers# injectable usage of >10 years, AdjOR = 0.55, 95% CI: 0.23 – 1.34, P-value for interaction = 0.19).

However, among heavy smokers, there appears to be a decreasing likelihood of developing CC as the length of use of injectable contraceptive increased. Current heavy smokers who used injectable contraceptive beyond 10 years had about 95% reduced odds (for current heavy smokers# injectable users of >10 years , AdjOR = 0.05, 95% CI: 0.004 – 0.70, P-value for interaction = 0.026) of developing CC as compared with non-smokers who never used injectable contraceptive (the reference group). Furthermore, the interaction between current heavy smokers who used injectable contraceptive for less than five years (for current heavy smokers# injectable usage of <5 years, AdjOR = 0.60, 95% CI: 0.11 – 3.29, P-value for interaction = 0.56) and heavy current smokers who used injectable for between 5 – 10 years (for current heavy smokers# injectable users of 5 - 10 years, AdjOR = 0.33, 95% CI: 0.04 – 2.70, P-value = 0.29), did not reach statistical significance There was however no interaction between smoking status and oral contraceptive use.

3.4.4 Case-control study III: Sexual, reproductive and hormonal factors as major risk factors of cervical cancer.

There were 3,546 CC cases and 2,560 appropriate controls for sexual, reproductive and hormonal factors as the major risk factors of CC.

Univariable analysis

Parity, number of sexual partnerships, age at first pregnancy, injectable contraceptives with increasing years of use, oral contraceptive after tenth year of use, tobacco smoking, age≥50 years, place of residence (Urban/Rural) and HIV status were individually associated with CC in Black South African women when sexual and reproductive behaviours were considered as the major risk factors of CC (Table 3.6). Also, participants who ever had Pap smear before their cancer diagnosis had lesser odds of developing CC as compared to women that never had Pap smear.(COR = 0.57, 95% CI: 0.48 – 0.67, P-value <0.001)

Table 3. 6: Crude and adjusted odd ratios of the risk of cervical cancer when sexual, hormonal and reproductive behaviours are the major risk factors (case-control study III)

	[1]Univariable logistic regression analysis			[2]Multivariable regression analysis		
Factor	**COR**	**95% CI**	**P-value**	**AdjOR**	**95% CI**	**P-value**
Age						
<50	1.00	Ref	Ref	1.00	Ref	Ref
≥ 50	0.78	0.71 - 0.87	<0.001*	0.68	0.59 - 0.78	<0.001*
Missing data	0.63	0.04 - 10.01	0.75	0.49	0.03 - 7.58	0.611
Parity						
0	1.00	Ref	Ref	1.00	Ref	Ref
1-2	4.25	3.21 - 5.62	<0.001*	3.06	1.94 - 4.84	<0.001*
3-5	5.47	4.14 - 7.24	<0.001*	3.85	2.42 - 6.10	<0.001*
6&above	5.81	4.39 - 7.70	<0.001*	4.54	2.85 - 7.25	<0.001*
Missing	11.56	6.57 - 20.34	<0.001*	10.55	6.05 - 18.39	<0.001*
P-value for trend			*<0.001**			*<0.001**
Marital status						
Single/Never Married	1.00	Ref	Ref	1.00	Ref	Ref
Married/Living together	1.43	1.25 - 1.64	<0.001*	1.22	1.05 - 1.43	0.011*
Widowed	1.15	0.99 - 1.35	0.067	1.01	0.84 - 1.22	0.878
Separated	1.39	1.16 - 1.66	<0.001*	1.23	0.999 - 1.508	0.051
Missing data	0.91	0.36 - 2.30	0.838	0.94	0.35 - 2.53	0.895
Age at first pregnancy						
≤16yrs	1.00	Ref	Ref	1.00	Ref	Ref
>16<21yrs	0.68	0.57 - 0.82	<0.001*	0.70	0.57 - 0.85	< 0.001*
21&above	0.53	0.44 - 0.64	<0.001*	0.57	0.47 - 0.70	< 0.001*
Missing data	0.25	0.20 - 0.32	<0.001*	0.59	0.39 - 0.88	0.010
P-value for trend			*<0.001**			< 0.001*
Lifetime number of sexual partners						
0-1 partner	1.00	Ref	Ref	1.00	Ref	Ref
2-5 partners	1.54	1.33 - 1.79	<0.001*	1.49	1.27 - 1.75	<0.001*
5 and above	1.57	1.28 - 1.93	<0.001*	1.64	1.31 - 2.05	<0.001*
Missing data	0.58	0.43 - 0.78	<0.001*	0.66	0.48 - 0.92	0.014
P-value for trend			*<0.001**			< 0.001*
Oral Contraceptives use						
Never	1.00	Ref	Ref	1.00	Ref	Ref
yes, <5years	1.22	1.04 - 1.43	0.015*	1.19	0.998- 1.413	0.052
yes, 5-10years	0.99	0.80 - 1.24	0.959	0.93	0.73 - 1.19	0.574
yes, ≥10years	1.29	1.02 - 1.63	0.037*	1.38	1.07 - 1.77	0.014*
Missing data	0.64	0.44 - 0.92	0.160	0.77	0.51 - 1.16	0.216
P-value for trend			*0.025**			*0.145*
Injectable contraceptives use						
Never	1.00	Ref	Ref	1.00	Ref	Ref
yes, <5years	1.21	1.06 - 1.40	0.007*	1.02	0.87 - 1.19	0.827
yes, 5-10years	1.36	1.1 - 1.64	0.001*	1.14	0.93 - 1.40	0.210
yes,≥10years	1.89	1.55 - 2.30	<0.001*	1.51	1.21 - 1.89	< 0.001*
Missing data	0.63	0.46 - 0.85	0.003	0.63	0.45 - 0.89	0.008
P-value for trend			*<0.001**			*0.003**

Table 3.6 continued

	Univariable analysis			Multivariable analysis		
Factor	COR	95% CI	P-value	AdjOR	95% CI	P-value
Educational qualification						
No education	1.00	Ref	Ref	1.00	Ref	Ref
Primary school	0.80	0.69 - 0.93	0.003*	0.76	0.65 - 0.89	0.001*
High school	0.69	0.60 - 0.80	<0.001*	0.64	0.54 - 0.76	< 0.001*
Tertiary	0.27	0.19 - 0.40	<0.001*	0.31	0.20 - 0.48	< 0.001*
Missing data	1.24	0.64 - 2.41	0.53	1.36	0.65 - 2.83	0.414
P-value for trend			*<0.001**			< 0.001*
Type of residence Urban/Rural						
Urban	1.00	Ref	Ref	1.00	Ref	Ref
Rural	1.35	1.19 - 1.54	<0.001*	1.16	1.01– 1.35	0.041*
Missing data	0.66	0.36 - 1.22	0.19	0.74	0.37– 1.48	0.398
Smoking status						
Never	1.00	Ref	Ref	1.00	Ref	Ref
Ex-smoker	0.95	0.81 - 1.12	0.552	1.08	0.90 - 1.29	0.391
Current light smoker (1-14g/day)	0.53	0.37 - 0.75	< 0.001*	0.56	0.38 - 0.82	0.003*
Current heavy smoke (>14g/day)	0.71	0.59 - 0.85	< 0.001*	0.72	0.59 - 0.89	0.002*
Missing data	0.95	0.47 - 1.95	0.893	1.04	0.49 - 2.18	0.922
P-value for trend			*0.052*			*0.847*
Snuff ever use						
Never	1.00	Ref	Ref	1.00	Ref	Ref
Ex users	0.91	0.78 - 1.07	0.243	0.89	0.76 - 1.06	0.195
Current users	2.06	1.77 - 2.40	< 0.001*	1.91	1.62 - 2.25	< 0.001*
Missing data	0.79	0.20 - 3.18	0.744	0.68	0.15 - 3.06	0.616
P-value for trend			*<0.001**			*0.019**
HIV status						
Negative	1.00	Ref	Ref	1.00	Ref	Ref
Positive	1.26	1.11 - 1.43	<0.001*	1.21	1.04 - 1.40	0.011*
Missing Data	1.45	1.19 - 1.76	<0.001*	1.45	1.17 - 1.80	0.001
Year of interview						
1995 – 2000	1.00	Ref	Ref	1.00	Ref	Ref
2001 – 2005	0.58	0.51 - 0.67	< 0.001*	0.62	0.53– 0.72	< 0.001*
2006 – 2010	0.96	0.85 - 1.07	0.448	0.97	0.84– 1.12	0.692
P-value for trend			*0.645*			*0.947*
Ever had pap smear						
Never	1.00	Ref	Ref			
≥1	0.57	0.48 - 0.67	< 0.001*			
Missing data	0.69	0.62 - 0.77	< 0.001*			

Hosmer-Lemeshow Chi2(8) = 10.9, P-value = 0.21. Multivariable Model built with: HIV, Age ≥50, Place of residence (urban/rural), Injectable contraceptives; oral contraceptive, year of diagnosis, age at first pregnancy, parity, marital status, tobacco smoking, snuff use, educational attainment, and sexual partnership. COR: crude odds ratio, AdjOR: Adjusted odds ratio

Multivariable analysis

The odds of developing CC increases with increasing number of lifetime sexual partners (P-value <0.001) but decreased with increasing age at first pregnancy (P-value <0.001). There was an increased odds of developing CC among women who used oral (AdjOR = 1.4 CI:

1.07 – 1.77, P-value = 0.014) or injectable contraceptives (AdjOR = 1.5 CI: 1.21 1.89, P-value < 0.001) beyond 10 years. Also, increasing length of educational attainment is protective against the risk of CC (Ptrend < 0.001). Women who were married or co-habiting had a 1.2 fold likelihood of developing CC as compared to single women (AdjOR for married women= 1.2. CI: 1.05 - 1.43, P-value=0.011). There was a slight increased odds of developing CC among rural dwellers as compared to women living in the urban areas (AdjOR= 1.16, CI: 1.01 – 1.35, P-value=0.041). Also, women older than 50 years had a 32% reduced odds of CC as compared to women in the reproductive age (AdjOR= 0.7, CI: 0.59 – 0.78, P-value < 0.001) (Table 3.6).

3.4.5 Post estimation diagnostics and sensitivity analysis for JCCCS sub-studies.

The data for the three JCCCS case-control sub-studies fit the multivariable models since the P-value of each Hosmer-Lemeshow test was greater than 0.05. For the multivariable models of the three case-control sub-studies, interviewer's code was removed because the VIF was greater than 10 which suggested collinearity with 'year of interview', which was related to the interviewer. The VIF for parity was higher than ten (15.4) in case-control study I (HIV study), but when parity was removed from the model, the odds ratio of the reproductive factors (marital status, lifetime sexual partners, age at first pregnancy, contraceptive use), HIV and smoking did not change significantly. Parity was therefore left in the models because of its strong link with CC based on the literature. All other variables had VIF values less than ten which suggest that there was no significant co-linearity among the variables. The AUC for models I, II, and III were 0.71, 0.67 and 0.65 respectively. Since these values are greater than 0.5 and they approach 1, we can reasonably state that the three models have high discriminating and predictive value. Also, the HIV model (CC I) best predicts CC risks in South Africa.

Sensitivity analyses:

After adding breast cancer participants to the control arm of the three JCCCS case-control sub-studies, the number of observations in the control arm of sub-study: I (HIV); II (tobacco smoking and alcohol use) and III (sexual and reproductive factors) increased to 4,454, 4,419 and 5,652 observations respectively (previously from 1,382; 1,327 and 2,560 observations respectively) (Figure 3.1). After sensitivity multivariable analyses with the new control

arms, there was no remarkable difference in the direction of the odds ratio of the variables of interest. Thus, they were not qualitatively different from the main model, except for oral and injectable contraceptives that did not have any association with CC in sub-study III (sexual and reproductive factors). These sensitivity results were presented as Appendices IV, V, and VI.

4 CHAPTER FOUR

DISCUSSION

4.1 Introduction

In this chapter, the results of the research were discussed in relation to findings from previous national and international studies on CC and within the context of South Africa. The strength and limitations of the study were also discussed to further guide the interpretation of our results.

We conducted for the first time in South Africa, temporal analyses of CC risks, incidence, mortality and survival spanning 19 years, by triangulation of three large databases: NCR (incidence, 1994-2009); Stats SA (Mortality, 2004-2012)); and JCCCS (risk factors, 1995-2010). We interpreted our findings with landmark events that can influence CC trends and risks in South Africa (Figure 4.1). Evidence on the interplay between these events is essential for planning and proper allocation of public health resources. Also, this study serves as a baseline for comparing the impact of future CC interventions in South Africa and elsewhere.

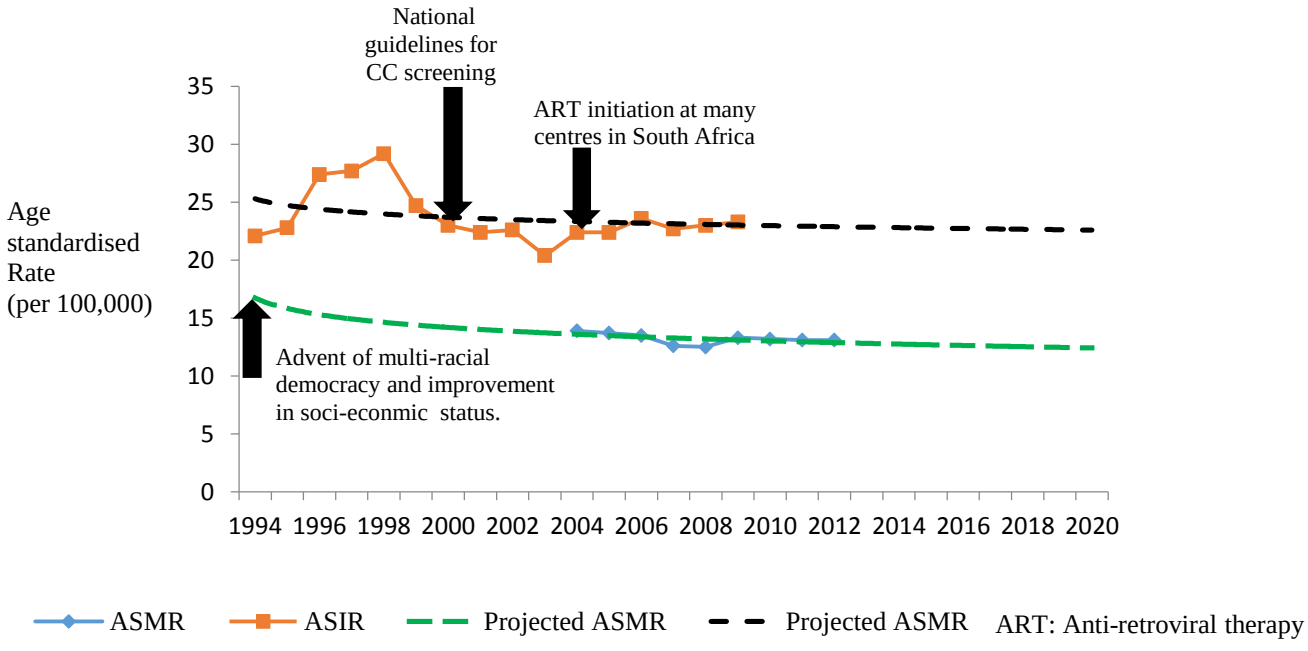

Figure 4. 1 Summary of events related to cervical cancer trends in South Africa (1994-2012)

Summary of main findings

Our findings showed that approximately 5,000 new cases of CC were recorded annually and almost 3,000 women died from CC every year in South Africa. Also, fluctuations occurred in CC incidence between 1994 and 2001 as reported to the NCR. However, from 2001 to 2009, there was a slight increase in CC incidence of about 0.9% per annum. On the other hand, the South Africa mortality rates as reported to the Stats SA declined by 3% per annum from 2005 to 2008 and subsequently increased by 0.8% per annum from 2008 to 2012.

Further, there was marked racial disparity in CC rates with Blacks and Coloureds having high incidence and mortality rates but low 5-year survival rates while Indians/Asians and Whites had opposite rates. However, during the study period, Blacks and Indians/Asians generally had increased incidence and mortality trends while Coloureds had declining trends. On the other hand, Whites had slightly decreased incidence but increased mortality rates.

The contiguous provinces of Mpumalanga, North West and Northern Cape, that also had international boundaries, had the highest tertile of mortality rates beyond 16 deaths per 100,000 women. Whereas, the neighbouring provinces of Western Cape and Eastern Cape had the lowest provincial mortality rates that was below 10 deaths per 100,000 women. It was also found that women of the reproductive age (15-49 years) accounted for almost half of CC cases and about a third of mortalities.

Among Black South Africans, the risk of CC increased from 2-fold during the pre-ART era to 3-fold during the ART era among. Also, parity was the strongest and most consistent reproductive factor associated with CC. A dose-response relationship was also found between tobacco smoking, snuff use and CC after controlling for cofounders. However, the initial relationship between alcohol and CC from univariable analysis was lost after controlling for confounders. There was no interaction between hormonal contraceptive use and HIV status, but injectable contraceptives had interaction with tobacco smoking that appears to be protective of CC among smokers.

4.2 Trends in the incidence and mortality of cervical cancer in South Africa

Incidence and mortality rates

The CC incidence (23.8/100,000 women) and mortality (13.1/100,000) rates in South Africa were lower than the rates in most LMICs in 2009 and 2012 respectively (1–4). In contrast, South African rates doubled the rates from most high-income countries (1–4,126). However, the WHO projected CC rates for South Africa that was based on reports from cancer registries of neighbouring countries was higher than the rates obtained from this study. For example, the mortality rate in 2012 was 13.1 per 100,000 women from Stats SA but 18.0 per 100,000 women from WHO projections (1). Although there may be some concern about the quality of national data in South Africa, it is still essential to evaluate CC burden and trends based on information from these repositories (NCR and Stats SA) to aid planning and policy formulation in the country. Moreover, South Africa health system and the socio-political situation is different from that of neighbouring countries (20,118).

Incidence trends

Our study showed that there was a sharp rise in CC incidence by about 7.6% per annum from 1994 to 1998 in South Africa. An increasing prevalence of HIV in South Africa at least 5-10 years earlier may be partly responsible (14,45,61,120). Also, the advent of multi-racial democracy in 1994 reduced barriers to reproductive health services, especially among the Black population, who contributed about four-fifth of the total CC incidence in this study (10,14,45,115). The increased healthcare access in South Africa during this period (1994-1998) might have increased the frequency of histological diagnosis of CC as reported to the NCR (115). However, the dramatic drop in the ASIR by about 8.5% per annum between 1998 and 2001 is difficult to explain. An explanation may be the suspicion that cancer cases were not adequately reported to NCR by the private laboratories during this period (116,118). However, this may not be true for CC since our study found that the proportion of CC cases reported by private laboratories increased from 7.9% in 1995 to 13.1% in 2003 with minimal annual percent change. Moreover, Singh et al.(116) also showed that the apparent drop in cancer reports by private laboratories from 2005 to 2007 had minimal effect on cancer incidence rates in the country (116). Nonetheless, such fluctuation in CC incidence

between 1994 and 2001 may still heighten the notion of under-reporting of CC during the latter period of 1998-2001 (35). However, since there was no such marked fluctuation in incidence after 2001, we can reasonably believe that there was improved data quality of the NCR afterwards.

Despite the initiation of a population-based CC screening program in 2000 and the national deployment of ART in South Africa in 2004, the incidence rates of CC increased by 0.9% per annum from 2001 to 2009 (Figure 4.1). However, the CC trends slowed down from 2001 to 2009 as compared to the trend from 1994 to 1998 (0.9% vs 7.9%). This reduced upward trend coincided with the commencement of the CC screening program in 2000. However, most studies from SSA during similar time periods reported markedly increased trends (6,64,65,127,128). It may be argued that the initiation of population-based CC screening program and a nation-wide roll-out of ART in 2000 and 2004 respectively, may not have meaningfully impacted on the evolution of CC in South Africa between 2000 and 2009, because premalignant cervical lesions usually progress to invasive CC after ten years (31,129). Nevertheless, marked decline in CC rates soon after the commencement of widespread CC screening had been severally documented elsewhere (36,49,79,130). For example, in Shanghai, China, the incidence rate of CC declined by 63% after a similar ten year period of initiation of CC screening program (1960-1970) (81).

The lack of a considerable decline in CC incidence in South Africa may be due to a number of reasons. CC screening program was not yet entrenched in South Africa, as the targeted 70% screening coverage rate for maximal efficacy (so as to achieve a 60% reduction in incidence) was not achieved in most provinces (10,90). The low coverage rate was due to inadequate health personnel and infrastructure, and poor awareness among the target women (10,90). Also, an initial paradoxical increase in CC incidence may occur soon after screening began because the screening program can, at first lead to increased diagnosis of early-staged CC cases (10,29).

The slightly increased incidence of CC between 2001 and 2009 also mirrored the complex interactions between HIV prevalence, ART availability and preventive programs of CC in South Africa. The widespread ART coverage in South Africa that exceeds 75% in 2011, increased the country's HIV prevalence rate by about 32% between 2002 (15.1%) and 2012 (19.9%), among individuals who were older than 24 years (14,20), since ART reduced

mortality among PLWHA (14,20). Thus, the increased CC rates between 2001 and 2009 partly echoed the increased HIV prevalence in the country. Scott Dryden-Peterson and co-workers also reported an increased trend in CC incidence after ART expansion in Botswana, a neighbouring country of South Africa with equally high HIV burden and no functional population-based CC screening program (64). In contrast, Uganda and Zimbabwe with high (but reducing) HIV burden, widespread ART coverage and relatively weaker health systems did not have similar pattern as South Africa (6,65).

Our findings from the case-control study (CC I) of HIV infection, as a major risk factor of CC among Black cancer patients in Johannesburg also reinforced the nexus between CC and HIV trends in South Africa. We found that the HIV prevalence among the Black CC participants was 22.9%, which was higher than the prevalence among Blacks who were older than 24 years in Gauteng province (18.8%), the site of the study (14). The HIV prevalence among CC patients in our study was similar to previous reports from elsewhere in SSA (30,58,131). Also, our results from the CC I (HIV) study showed that the association between CC and HIV infection increased from about two-fold during the pre-ART era (1995-2004) to three-fold during the ART era (2004-2010). This odds of CC in HIV-positive women approached the stronger association (odds of about 5) reported from high-income countries, which previously had wider ART coverage as compared to LMICs (45,55,57,59,60,129,131). Our study therefore, suggests that ART may be a major driver of increased CC risk among HIV-positive women, because lower association (between 1.5 and 2) was previously reported from South Africa and elsewhere in SSA during the pre-ART era (30,120,132,133). We also found that the likelihood of diagnosing CC among women older than 50 years as compared to women of the reproductive age (15 – 49 years) increased during the ART era as compared to the pre-ART era. The preceding suggests that CC rates are likely to increase among older PLWHA (and indeed in the general population) as access to ART increases. A similar increase in CC rates among women older than 50 years was observed in Zimbabwe and Uganda (6,65).

Although the advent of ART dramatically reduced the incidence of other AIDS-defining cancers like non-Hodgkin's lymphoma and Kaposi sarcoma, the impact of ART and the trends in CC incidence remains unclear (63,129). Several workers have demonstrated that ART reduces HPV persistence and increases the rate of regression of pre-cancerous lesions

(60,62). Also, ART stimulates immune reconstitution that should theoretically prevent CC (62,129). However, PLWHA on ART still have chronic latent defective immunity that predispose them to CC at an older age (55,59,60,64). Interestingly, emerging in-vitro evidence shows that some anti-retroviral drugs (especially protease inhibitors) have some therapeutic anti-CC effect at the onco-genetic level (134). Nevertheless, current empirical evidence calls for concerted CC surveillance among PLWHA (including those on ART).

Mortality trends

For CC mortality trends in South Africa, we found that the overall ASMR slightly declined by 0.6% per annum from 2004 to 2012. The overall slight downward mortality trends in South Africa was opposite to the upward trends in SSA (25,128). However, Brazil - another middle-income country like South Africa - had a comparable declining trend of about 0.2% per annum during similar time period (2003 – 2012) as our study (135). In contrast, the downward trends in South Africa was relatively slower as compared to rates from many high-income countries (4,22,42,126). Two phases of mortality trend was however observed in South Africa. The first phase was a decline at 3% per annum from 2004 to 2008 and the second phase was an increase of 0.8% per annum from 2008 to 2012. Such pattern previously occurred in some high-income countries because of sporadic shift in risk factors and screening practices (22,126,136). The initial decrease in mortality from 2004 to 2008 in South Africa can largely be attributed to the initiation of ART in South Africa in 2004 (19,20,61). At that time, HIV infection was a leading competing cause of death in South Africa (19,20,112). Hence, the roll out of ART in 2004 halted the quick progression to death of PLWHAs (who could also have CC) that were hitherto not on treatment (19,20).

The slightly increased trend in mortality between 2008 and 2012 may be because those PLWHAs with CC on ART eventually succumbed to the cancer. The mortality increase in the latter phase may also be due to improvement in reporting of cancer mortalities in the country (137). In addition to the foregoing, we however speculate that the later increase in CC mortality between 2008 and 2012 after increased ART coverage can also be because the improved quality of life in PLWHA unmasked the background mortality risk that is directly related to co-morbid chronic diseases that are complications of ART or direct cause of the ongoing demographic and health transitions in South Africa (18–20). Nevertheless, the overall downward mortality trend between 2004 and 2012 in South Africa may suggest some

improvement in oncology care after the advent of multi-racial democracy in South Africa in 1994, since attempt were made by South African government to reduce the inequity related to healthcare access in the country (10,18,115). Also, population based CC screening can reduce the prevalence of late staged CC, thereby contributing to improved survival and reduced mortality (4,10,29,57,79,138).

Racial disparity in cervical cancer trends

Our study found marked racial disparity in the rates of CC in South Africa. The South African Indians/Asians and Whites had relatively low rates (incidence and mortality rates of 10-11 and 2-4 per 100,000 respectively), that were similar to rates from high-income countries. However, Blacks and Coloureds had relatively high rates (incidence and mortality rates of 17-26/100,000 and 9 – 15/100,000 respectively) that approached the rates from LMICs (1–4,6). The roll out of ART in 2004 coincided with a significant decline in mortality rates in only Blacks and Coloureds from 2004 to 2008. This is not surprising since these two population groups had the highest HIV prevalence in the country (14). However, mortality rates increased from 2008 to 2012 in Blacks possibly because PLWHA with CC eventually succumbed to the cancer or because of improved cancer reporting. However, the continued decline in rates in Coloureds throughout the study period is surprising and needs further evaluation. In contrast, the Indians/Asians and Whites had low rates but Indians/Asians had increased rates while Whites had slightly decreased incidence rates between 2001 and 2009 and slightly increased mortality rates from 2004 to 2012. This suggests a stall in the trends among Whites and a reversal of trends among the Indian/ Asians since both population group previously had marked reduction in mortality rates between 1949 and 1990 (16,22). Thus, there may presently be complacency in preventive efforts among them. Nevertheless, the relatively low and stable incidence rates in Whites suggests that women in LMICs can be free from the scourge of CC, given appropriate preventive programs that are comparable to what obtains in the high-income countries. The racial disparity of CC trends in South Africa contrasts with the trends in the United States of America (USA) where rates in all population groups declined considerably during similar time period as South Africa (36,42,139).

The poor 5-year relative survival rates among Blacks and Coloureds (45-55%) were similar but higher than the reported rates in the LMICs (6,103,106). However, the high relative

survival rates of between 60% and 80% that we found among Indians/Asians and Whites were comparable to rates in high-income countries (6,103). Our study utilised the complement of MR: IR ratio to estimate relative survival rates and obtained values that were comparable to rates from other LMICs and high-income countries, that utilised the traditional methods of survival estimation (29,42,96,100,103,106,140). For example, the 5-year relative survival rate for Zimbabwe (44.1% for Blacks and 60.9% for Whites) and Brazil (58.8%) was also similar to the South African rates for Blacks and Whites (106,140). Nonetheless, we believe that the wide difference between our relative survival estimates and the report from a population-based cancer registry in Uganda (19.8%) that also utilised traditional survival analysis method (cohort method) may be because their study was biased by high loss to follow – up of about 36%, coupled with the fact that South Africa has stronger health system. Moreover, the Ugandan survival estimate was conducted in 1999, about five years earlier than our study period (2004 – 2009). Mortality to incidence ratio is a more sensitive tool, (as compared to only incidence or mortality) for evaluating the quality of cancer care (41,105). This ratio may therefore be a reliable tool for crude estimation of CC survival rates, especially in countries without good cancer follow-up and linkage (41,105).

It appears that the low incidence and mortality rates and high survival rates in Indians /Asians and Whites were due to different reasons. The rates among Indians/Asians could be due to less risky sexual behaviours and low HIV and smoking prevalence among them (4,14,16,115). Whereas, higher socio-economic status, easy access to healthcare facilities (especially screening facilities), low parity and low HIV prevalence could account for the low rates in Whites (4,14,16). Also, Indians/Asians and Whites may present to hospital with early staged disease that is amenable to curative treatment thereby increasing survival rates in them (6,103).

In contrast, Blacks and Coloureds had higher incidence and mortality rates because they had: relatively poor access to healthcare and CC screening, low socio economic status and high prevalence of HIV, tobacco smoking and teenage pregnancy (4,10,14,16,119). The modest increase in survival rates in the general population (13%) and especially among Coloureds (8.8%) and Blacks (7.6%) between 2004 and 2009 may suggest that there was some improved access to CC down staging procedures, oncological care and ART. This study

highlighted the usefulness of conducting differential analysis of CC rates by population groups (rather than relying on overall rates), so as to target interventions according to the peculiar needs of each vulnerable group (20). Emerging evidence suggest that a contributory factor to racial disparity of CC rates is genetic polymorphism among population groups (51). Such genetic information can aid the design of a targeted, cost-effective, CC risk assessment among the vulnerable population group (51). Nevertheless, the impact of such genetic information may not supersede the current evidence-based preventive interventions and concerted efforts aimed at reducing racial socio-economic and healthcare inequity, that is presently believed to be the driver of racial disparity of CC evolution (10,20,36,138,139).

Temporal trends in age at diagnosis and age at death

CC was hitherto rare in women younger than 35 years because its natural history suggests that there is a latency period of at least 10-20 years between sexual debut and its evolution (33,34). However, our study found that about half and one–third of CC cases and mortalities occurred in women of the reproductive age (15-49 years). Furthermore, the three case - control studies from the JCCCS study showed that women older than 50 years had 18-38% reduced risk of developing CC as compared to women of the reproductive age (15 – 49years). Another disturbing finding was that the incidence and mortality rates among women between the ages of 25 and 34 years increased during the study period. This pattern was also noticed by previous workers (48,117,124,127). But opposite trends occurred in some Southern African Development Community (SADC) countries and most high-income countries (2–4,6,65). The increasing rates of CC at young age below 35 years in South Africa may be due to the high prevalence of HIV, poor screening of young women, decreasing age at sexual debut and prevalent teenage pregnancy (22,47,48,81). However, initiation of ART in 2004 could have accounted for a reduction in mortality rates among women aged 20-24 (AAPC= -4.5%). A decline in CC rates among women aged 50- 64 years during the study period may suggest that older women in South Africa have higher screening rates and lesser HIV prevalence (10,14,37,48). Moreover, opportunistic screening might have occurred in older women during their post-natal and gynaecological consultations (10).

The age-specific incidence and mortality rates in the White population increased from 19 years and had a slight steady decline in rates from 40 years till 70 years. This may suggest that adequate CC screening was commonly commenced among the White population

between the ages of 25 and 30 years (which was about 10 years earlier than age 40) to keep the incidence stable from age 40 years. In contrast, the age specific rates in Blacks and Coloureds was higher and it increased from 19 years till 65 years as was found among the Black population group in Harare during similar study period (65). The National screening guideline that recommends commencement of screening at 30 years may be appropriate in the White population based on our finding but may not be suitable in the Blacks and Coloureds that have high age-specific CC and HIV prevalence rates. The sharp decline in the age specific incidence rates beyond 65 years might be due to poor ascertainment in the elderly since histological diagnosis may not be conducted at that age (107,118). But, the age-specific mortality rates increased abruptly in the elderly as a result of the established relationship between old age and cancer mortality (64).

Province and cervical cancer

Previous workers identified factors responsible for inter-regional variation of CC rates to include: high risk HPV and HIV prevalence, CC awareness and screening rates, barriers to health care, risky sexual behaviours, tourism industry, migration and socio-economic variations (4,22,23,42,43,59). Our study revealed that provincial mortality rates in South Africa are a complex interplay of multiple risk factors. Western Cape and Gauteng provinces were the least deprived provinces according to the South African index of multiple deprivation (SAIMD) (90). This correlated with their least CC mortality rates of less than 10 per 100,000 women in 2012. In contrast, Eastern Cape was the most deprived on the SAIMD scale but also had low rates of less than 10 per 100,000 women (90). The activities of an active cancer surveillance registry in Eastern Cape might have engendered CC awareness among the predominantly rural province (90). Furthermore, migration of young, active population of Eastern Cape (who were at increased risk of CC) to seek employment in other cosmopolitan provinces can also partly explain the low CC age standardised mortality rates in the province (127). However, conflicting reports exist about the state of under-reporting of cancer mortality records in the Eastern Cape which may bias our finding (20,90). In-migration across the borders of South Africa may also play a role in the geographical pattern of CC mortality since all the three provinces with the highest mortality rates above 16/100,000 in 2012 (MP, NW and NC) had international boundaries with Swaziland, Mozambique, Botswana, and Namibia. Further studies are needed to investigate

the suspected influence of trans-border migration on CC rates in South Africa. Moreover, migrants elsewhere were found to have poor CC screening rates and outcomes because of barriers to healthcare (23).

HIV is the leading cause of premature mortality in all the provinces of South Africa (19,20). Thus, provincial HIV prevalence and CC screening rates may partly explain the CC pattern in the provinces. For example, Mpumalanga province had the second highest HIV prevalence rate of 14.1% (14) and a moderate CC screening coverage rate of 54.9% (90). This may partly explain the high CC mortality rates of 19.8 per 100,000 women in the province since the screening rate apparently did not match the impact of high HIV prevalence rate in the province. Although, tourism activities increased CC rates in the coastal regions of Spain (22), but the coastal provinces in South Africa had disparate rates. However, in addition to having the highest HIV prevalence rate, KwaZulu-Natal province also have a thriving tourism industry that may affect sexual behaviour and contribute to high CC rates in the province (22,90). But a very high CC screening coverage rate in the province might have reduced the mortality rates to intermediate rates of between 10 and 15 deaths per 100,000 women (90).

However, spatial analysis at district or sub-district level will further clarify the provincial mortality pattern by revealing intra-provincial clustering of cold or hot spots (19,138). Our study showed that other anonymous environmental factors may play a role in CC mortality as there were broad geographical belts of CC mortality, despite contrasting prevalence of known risk factors of CC. The geographical variations that we found in this study may also be related to the awareness and commitment of the leadership of each province towards the fight against of CC (10,59,90). Thus, operational research that may possibly entail mixed method approach is imperative to evaluate the provincial political will to combat CC. The geographical variation in the prevalence of HPV could also account for the provincial mortality pattern in South Africa but such information is not available (35).

Trends in histological types

In contrast to reports from high income countries, where there was decline in the incidence rate of SCC but an increase in the rates of ADC, due to poor sensitivity of Pap smear to ADC (35–37), the ASIR of SCC increased annually by 1.4% between 2000 and 2009 in South Africa. In contrast, the ADC rates were relatively stable, but had a downward trend

(AAPC= - 0.3%). This may suggest that the screening program that was commenced in 2000 created awareness and increased diagnosis of early staged SCC (Down-staging) (138). The downward trend of ADC may suggest that Pap smear screen was effective against ADC among the South African population (99).

4.3 Risk factors of cervical cancer among Black South African women

Tobacco and alcohol use and cervical cancer

The prevalence of tobacco smokers among CC mortalities (15.8%) in the Stats SA data and among the JCCCS participants (21.1%) was about two- and three-fold higher than in female South African population respectively (7.9%) (21). We also found from the smoking and alcohol risk study (case-control study II) that the odds of CC among smokers as compared to non-smokers was about two fold, and there was a dose-response association between tobacco smoking and CC. Our result was similar to report of previous workers (13,66,67), but slightly higher than previous results of the JCCCS (adjusted odds of 1.5) from 1995-2004 (13). The higher risks in our JCCCS participants that covered from 1995-2010, may suggest that tobacco control has not adequately impacted on CC risks, six years after the last study (13,125). The effect of smoking control efforts on CC may be delayed because of the long latency period of cancer evolution (125). More so, the female smoking rate appears not to have dramatically reduced as the rate was about 10.3% in 2002 (13) as compared to the current rate of 7.9% in 2012 (21).

Smokeless tobacco usage can also contribute to CC prevalence as about 30% excess risk of CC occurred among current snuff users as compared to never users in our study (CC II). We also found that ex-smokers and former snuff users had no difference in risk with never smokers or none users of snuff. Ruora et al (66) similarly found that there was no difference in CC risk among never smokers and ex-smokers among European women. This evidence is a good incentive to smokers to initiate the process of quitting. These findings emphasise the importance of intensifying holistic public health interventions on tobacco (including smokeless tobacco) control (66,67). Future study of the risk of CC and smoking is warranted to monitor the impact of control initiatives.

Consistent with previous studies, we found no association between alcohol use and CC after controlling for confounding variables (68,73). Issues related to social desirability can bias our result as the women may understate their alcohol consumption rate (14,78,121). Although, the pathophysiology of the link between cancers and alcohol consumption is still not clear, nonetheless, since current evidence confirmed strong associations between alcohol consumption and breast cancer and some HPV related cancers (oropharygeal, larynx) (122), coupled with the univariable association observed from our study, we posit that continuing surveillance of the impact of alcohol on CC risk is imperative (122).

We found an artefactual protective association between HIV positive status and CC in our smoking and alcohol risk case-control study, because the study was primarily designed to evaluate smoking and alcohol risks. This echoed the danger of obtaining wrong conclusions from the JCCCS study if appropriate design and eventual stringent exclusion of cancers that have association to the risk factor under investigation is not strictly adhered to (85,120).

Sexual and reproductive behaviours and cervical cancer

Of all the sexual and reproductive factors available in our JCCCS dataset, we found that high parity consistently had the strongest association with CC (adjusted odds of 3-5), based on the results of the three case-control studies. This is in agreement with reports from other studies (82,141). Thus, fertility control initiatives is a key preventive method of CC (30,39,76,77,85). This study further suggested that women with higher parity should be targeted for screening interventions. Two mechanisms have been described for the link between parity and CC (77,141). Firstly, repeated vaginal delivery can cause recurring cervical injury, that predisposes to increased risk of HPV infection and persistence (77,82,141). Also, recurrent cervical injury from multiple vaginal delivery can initiate mutation of cervical cells and carcinogenesis in the presence of HPV infection (77,82,141). It is therefore not clear if women that had multiple caesarean sections had a lower risk of CC as compared to those that had only vaginal deliveries (82,141). A knowledge of the mode of delivery (vaginal delivery vs caesarean section) of the JCCCS participants can assist to further clarify the role of cervical injury in cervical carcinogenesis and to aid counselling of women about their risks (82,141). However, such information was not available for analysis.

Secondly, pregnancy stimulates the production of high concentrations of oestradiol, that can directly aid HPV persistence or cause cervical ectropion (external protrusion of inner, columnar cervical cells or endocervix) (77,141). Cervical ectropion exposes the inner endocervical cells to external impact that predisposes the cervix to HPV infection and persistence (77,141). Also, cervical ectropion can undergo cellular transformations (also known as metaplasia) to initiate the process of carcinogenesis (141).

As for other sexual and reproductive behaviours, our case-control study III on sexual and reproductive factors showed a protective benefit of CC development among women who had delayed age at first pregnancy (Ptrend = 0.033). This result was similar to reports obtained from previous studies (30,76,77,82). Our finding further lends credence to the multiple benefits of programs aimed at reducing teenage pregnancies in the country (77,90). We also found that the likelihood of developing CC increases with increasing number of lifetime sexual partners. However, the association between the number of sexual partnerships and CC (odds ratio of about 1.5) was similar to a report from West Africa (30), but weaker than a previous report of the collaborative study on sexual and reproductive behaviours (odds ratio of about 3) (76). This study's lower point estimate may be because women in SSA are likely to understate their number of lifetime sexual partners because of issues of social desirability (78). Our study have been able to comprehensively describe the current associations between sexual and reproductive behaviours and CC in South Africa to enrich national evidence, as the previous collaborative analysis on reproductive risk factors of CC, that was conducted about 10 years ago (2006), excluded the JCCCS data because there was no information on "age at sexual debut" (82).

Hormonal factors and cervical cancer

As compared to never users, our case-control study III (sexual and reproductive factors) revealed that women that used hormonal contraceptives beyond 10 years had 1.3 to 1.5 fold increased likelihood of developing CC. This study from 1995 to 2010, was in agreement with a previous study from the JCCCS that evaluated data from 1995-2006 (85). But other previous studies showed conflicting report (28,77,84–86). While Roura et al (28) and a pooled analysis (84) found that combined oral contraceptive users beyond 10 years, had 1.4 to 1.8 fold increase in CC risk, Jensen et al(141) and Castle et al(142) found reduced risk (odd ratio of 0.54) and no association among their respective cohorts. Smaller sample sizes

may be responsible for the difference. The studies by Jansen et al (141), (n=312) and Castle et al(142), (n=499) had relatively smaller sample of cases than our study (n=3,546) and others that were in line with our results (28,84).

However, previous workers found marginal risk (of less than 1.5) of CC among prolonged injectable users (84,142). The link between CC and hormonal contraceptives is also related to estrogen elaboration as already described above for parity (77,84,141). School girls in South Africa that accept sub-dermal progesterone contraceptives may be exposed to progesterone for an extended period of their reproductive life (77,90). This study therefore highlights the need for proper counselling of young women and others about the associated risks of CC in relation to extended use of hormonal contraceptive. Appropriate CC preventive programs should therefore be introduced to them (79).

From case-control studies I (HIV) and II (smoking and alcohol), we found that there was no interaction between oral contraceptives and HIV or smoking status in the evolution of CC. However, while we found that there was no interaction between HIV status and injectable contraceptives, the interaction between smokers and injectable contraceptives appears to be generally protective. Our findings therefore contrast with previous the hypothesis that hormonal contraceptives (especially combined oral contraceptives) can potentiate HPV persistence in PLWHA or smokers (69,84,86). Our result should be reliable because of our large sample size and we adequately corrected for sexual and reproductive factors after stringent control selection. The result of this study is therefore reassuring since family planning is one of the major pillars of Prevention of Mother to Child Transmission of HIV (PMTCT)(86). Thus, HIV positive women and smokers in the reproductive age can be appropriately counselled that they have similar risk of CC as other women that used injectable contraceptive. This will ensure adequate contraceptive method mix among them. However, HIV positive patients should still be counselled on dual contraceptive protection with condom to reduce cross infection of HIV strains and HPV transmission (83).

Socio-demographic characteristics and cervical cancer

All the three case-control studies found that increasing level of educational attainment is protective of CC. Also, the majority (63.7%) of women that died from CC as reported to the Stats South Africa had less than nine years of education. These findings are in agreement with studies from both high income and LMICs (39,85). Higher educational attainment of women can lead to

economic empowerment, improved awareness of CC screening, ability to delay the age at first pregnancy and also limit family size. All these factors reduce the risk of CC (22,39,85). Thus, further investment in education of the girl child can positively impact on CC rates in South Africa (90).

Furthermore, results from the three case-control studies also showed that women living in the rural areas had higher risks of CC as compared to women living in urban areas. Most previous studies also found similar risks among rural women (53). This may not be far-fetched, since rural women are usually not economically empowered, oblivious of screening opportunities and may have barriers to health care (23,53). In contrast, higher CC risks were found among urban women in Netherlands because of sexual permissiveness (23).

Women who were married or living together with partners (co-habiting couples) had increased odds of CC as compared to never married, single women (adjusted odds ranges from 1.2-1.5), from results of all the three case-control studies. However, previous studies showed conflicting results (30,47,82,139). Married women are likely to be multiparous and therefore at increased risk of CC (82). However, the increased risk of CC in unmarried but co-habiting couples in our study paralleled the increased risk and prevalence of HIV in this group of couples in South Africa (14). Thus, it was previously highlighted that efforts should be geared towards removing barriers to marriage in South Africa (such as waiver of high bridal price), so as to reduce the prevalence of co-habiting couples and HIV prevalence in South Africa (14). Such socio-cultural transformation will also impact positively on the risk of CC in South Africa. Widows were expected to have increased risk of CC, as elderly widows are at increased risk of cancers on account of age and young widows might have lost their husband to the HIV scourge and may likely be HIV positive too. (19). Also, widows may be less empowered and therefore have increased barriers to healthcare and screening facilities. However, our study did not find a difference between CC risks in widows and single women.

Pap smear and cervical cancer

Expectedly, we found from univariable analyses of the three case-control studies that women who ever had Pap smear before developing CC were about 30 to 50% less likely to develop CC as compared to women who never had screening Pap smear. Our suspicion that Pap smear can

engender increased diagnosis of early staged CC was corroborated by the fact that another quarter of the participants had diagnostic Pap smear (130). We found that introduction of Pap smear did not change the odds of CC among HIV positive patients during the ART era (2004 - 2010). This may suggest that HIV women had similar screening pattern as the general population at that time. Thus, the impact of the current recommendation that PLWHA should have annual CC screening can be evaluated in future studies.

Temporal trend of cervical cancer in JCCCS study

There appears to be temporal trends in CC I (HIV) and CC II (smoking) studies since the "year of interview" generally had statistically significant estimate and its global P-value for trend was statistically significant (Ptrend < 0.001) (19). We found that there was a reduced likelihood of diagnosing CC after commencement of CC screening program in year 2000 (2001-2005 and 2006-2010) as compared to the period before year 2000 (1995-2000) in all the three models. Also, the odds of diagnosing CC increased during the ART era (for "2006-2010", Adj Odds: 0.6) as compared to the pre-ART era (for "2001-2005", Adj Odss: 0.43) Introduction of Pap smear in 2000 may be partly responsible for the reduced CC risks after 2000 while the relative increased risk from the time period 2006-2010 as compared to 2001-2005 may be the impact of ART as previously described above. Notwithstanding this seemly fitting explanation of the CC trends, we recognise that the observed trend in CC risks is a complex interplay of multiple risk factors, preventive efforts and concerns related to the study design and sample collection over time. For example, the trend might have been affected by the lower sample size of the initial time periods since this is an ongoing cumulative study. Nevertheless, we believe such bias will be non-differential for all the cancer patients who are also controls in this study. We therefore reasonably believe this trends pattern was valid.

Institution of death

The Stats SA mortality data revealed that about three-fifths (62.4%) and one-fifth (21.9%) of CC patients died in the hospital and at home, respectively. Similar pattern also occurred among cancer patients in England between 2006 and 2010 (143). It is not clear if patients

that died at home in our study had adequate end of life support. Further studies about end of life facilities for CC patients in South Africa should be conducted to improve care.

4.4 Strengths of the study

Both NCR and Stats SA national datasets are generalisable to the South African female population. Also, the point estimates, with generally narrow confidence intervals from this research should be reliable since all the three datasets had large number of observations ranging between 10,000 and 75,000 observations. Our study also showed differential rates that are not usually obtained from WHO estimates of CC rates for South Africa. Such differential rates are very useful for targeted interventions.

The selection of the controls for the case-control studies among other cancer patients in the JCCCS helped to obviate referral and recall (information) bias that is common with hospital-based case-control studies (73,85). In order to properly evaluate the risk of CC, we excluded cancer cases that had associations with CC and any risk under consideration. Thus, we designed and conducted three case-control studies based on the risk factor under considerations, so as to properly quantify the impact of the risk factors of CC in South Africa. Also, the triangulation of the three datasets to assess the trends and determinants of CC over a 19 year period (1994-2012) greatly improves the validity (internal and external) of the study. We found concordance in the findings from the three datasets that were collected for different purposes. Also, missing data for most variables in the JCCCS, NCR and Stats SA were less than 4.5% (except for HIV status in JCCCS and marital, educational and smoking status in the Stats SA dataset).

4.5 Limitations of the study

The results from this study should be interpreted in the context of its limitations**.** We recognise the inherent limitation of secondary data analyses with temporal components. Such limitations include issues of missing observations, missing variables, some misclassifications and changes in data entry methods and style over time (16,35). Since NCR is a pathology-based registry, all CC patients without histological diagnoses are not included in the registry thereby leaving out the 'Death Certificate Only (DCO)' category (65,106,107). Under-reporting of cancer cases to NCR by private laboratories was suspected between 2005 and 2007 (116,118). Similar under reporting and misclassification of cancer

deaths may have also occurred in Stats SA data (20). This can cause a bias towards the null and in the racial incidence and mortality rates since the proportion of racial DCO and unreported cancer mortality is unknown. The number of unspecified deaths may also cause bias. Since NCR is a passive cancer surveillance system (as opposed to active surveillance) some cancer cases may be missed.

However, there has been a marked improvement in the rate of reporting of deaths to Stats SA (119). Thus, the incidence and mortality rates obtained from this study are the minimal rates for the country which is still unacceptably high. Nonetheless, since the cervix is relatively accessible, most patients might have had histological diagnosis and the proportion of CC cases as reported by private laboratories did not suggest dramatic changes from our study. Also, Singh et al showed that the suspected drop in cancer reporting by private laboratories had minimal effect on the incidence rates in the country (116). Considerable missing value of the sociodemographic variables of the Stats SA may affect conclusions of the relationship of those variables to CC mortality. However, the result from the JCCCS study that showed reasonable concordance obviated this concern. Furthermore, the triangulation of the three datasets and the agreement of the results obtained from them reassured us of our conclusions. We utilised a population denominator of females ≥15 years as opposed to ≥20 years used by some studies because of the increased risk of cervical cancer in younger women due to the high prevalence of HIV in South Africa. Since age-standardised rates were used, our results should still be comparable to those of other studies. We utilised the complement of MI:IR ratio as a crude estimate of the relative survival rate and we recognise that it should not replace the time-honoured methods of cancer registration and follow-up where feasible. Also, we were unable to relate our survival rates with the cancer stage because such information was not available. Join point regression modelling would have been used for the trend analyses but we currently do not have access to the software. Join point regression analysis correct for marked changes in trends and points of inflection since such changes can affect the eventual AAPC and interpretations (108). To produce comparable and valid results, we visually inspected our trends and conducted partitioned trend analysis with linear regression to obviate for such bias (125). Also, we utilised the "vce (robust)" option in Stata to further obviate for any violation of linear regression that may be occasioned by sudden variations in rates over time.

It is desirable to include the HPV status of respondents in the risk factor analysis of JCCCS study (28). However, we utilised surrogates of HPV infection such as sexual, reproductive behaviours and HIV status in our model (28,66,67). HIV specific parameters such as time of HIV diagnosis, CD4 count, viral load, type and time of commencement of ART are essential variables that were not available for most participants of the study. Since the JCCCS study was conducted in Black women at a cosmopolitan province of Gauteng, the results of our case-control studies may not be generalisable to all South African Blacks that lived in less endowed provinces of South Africa. However, the hospital where the study was conducted was the largest oncological centre in the country and received referrals and treat cancer patients from all the provinces. The demographic differences between the respondents and non-responders in the JCCCS study was not known (85,121). Nevertheless, the JCCCS database had been useful in describing valid risk factors of cancer in South Africa and previous workers on the JCCCS database found no significant difference in demography between responders and non-responders (85,121).

Issues related to social desirability may affect respondents' answers to intimate questions in the JCCCS study. Women in SSA are likely to understate the number of lifetime sexual partners thereby leading to non-differential misclassification that can underestimate the point estimate (30,78). This can lead to bias towards the null in evaluating the number of sexual partners and its association with CC.

Ideally, participants in the JCCCS who had total hysterectomy (removal of the uterus including the cervix) should be excluded from the study population since such individuals are not at risk of CC (16). The South African population denominators that we utilised for trend analyses should have been corrected for national hysterectomy rate. But such data was not readily available. Thus, if the uncorrected hysterectomy rates is considerable, then our current results may be an under estimate of the true rates.

5 CHAPTER FIVE

CONCLUSIONS AND RECOMMENDATIONS

The conclusions and recommendations to assist policy makers are presented. Future research opportunities are also highlighted.

5.1 Conclusions

We have evaluated the trends and determinants of CC in South Africa to inform policy review and targeted intervention. The increased rate of CC incidence in South Africa from 2000 – 2009, despite commencement of CC screening program appears to mirror the increased ART coverage and prevalence of HIV in the country. There was an increased risk of CC among Black South African women after the introduction of ART. Thus, an increasing access to ART in South Africa can paradoxically increase the burden of CC in South Africa. Also, there was marked racial disparity in the CC rates with Blacks and Coloureds having high rates in contrast to Whites and Indian/Asians with low rates. The low incidence rates in the White population showed that, given appropriate preventive interventions, women in the LMICs can be free from the scourge of CC.

A considerable proportion of the CC cases and mortalities were women of the reproductive age and the rates increased among women younger than 35 years. This contrasts largely with reports from high income countries where CC is commoner among the elderly. The provincial mortality pattern appears to be a complex interplay of multiple factors that may include HIV prevalence, CC screening coverage rate, socioeconomic indices and migration.

This study, for the first time in South Africa showed that there was an increased likelihood of CC among snuff users (1.3 fold). Also, tobacco smokers in South Africa have similar risk (doubled risk) of CC as women in high-income countries. Furthermore, PLWHA who used hormonal contraceptives have no demonstrable extra risk of CC than HIV negative women, but hormonal contraceptives usage appears to reduce the risk of CC among smokers. There was no association between CC and alcohol use after controlling for confounders. Parity of

the women was the most consistent reproductive factor associated with CC after controlling for cofounders.

We have generated a number of hypotheses aimed at better understanding of the changing epidemiology of CC in South Africa and globally. There is therefore urgent need for a review of the CC control program in South Africa and further researches on the epidemiology of CC in South Africa.

5.2 Recommendations

The following are some recommendations based on the results of this study.

1. Review of cervical cancer screening

The above-mentioned results of this research suggest that health policy makers in South Africa should holistically review the current CC control guideline based on available evidence in the context of the socio-economic realties, HIV prevalence trends and ART coverage rate of the country.

(a) Downward review of age of commencement of CC screening

We recommend that the current national CC screening policy should be reviewed by reducing the age of commencement of screening to cover young women below 30 years. This is because our study has shown an increasing trend in CC rates in women younger than 35 years and the process of carcinogenesis would have commenced about 10-15 years earlier. Although, there are concerns about poor sensitivity of Pap smear and eventual over diagnosis, inappropriate treatment and heightened anxiety among women younger than 25 years (34), present realties in South Africa as expounded by our result weighs more towards early initiation of CC screening possibly at 25 years.

(b) Reduction in the screening interval of CC screening

We also recommend that the current screening interval be reduced from 10 years to possibly five years because our study showed an increasingly strong association between HIV (and even ART) and CC in the country, and coupled with the following background facts: (i) South Africa has one of the highest global prevalence of CC and HIV infection can reduce the interval of progression from premalignant to malignant state of the disease (14,47,55,60,98) (ii) Although, South African national guideline for HIV positive women

recommends annual CC screening among them, a significant percentage of HIV positive women in the country will not benefit from the intensive screening program because they are yet to be diagnosed. (iii) Moreover, a significant proportion (34%) of PLWHA, newly diagnosed of cancer were not aware of their retroviral status before the cancer diagnosis (121) and (iv) the HIV infection process is dynamic with several unknown new infections occurring daily coupled with sub-optimal HIV testing rate in the country (121). Based on the aforementioned and the grounded epidemiological "tip of the iceberg" principle, a significant number of undiagnosed HIV positive women will be missed by the current general population screening of ten years. In fact, a more regular Pap smear screening program can be linked with the provider initiated HIV testing and counselling (PITC) program thereby expanding opportunities for radically increasing the rate of HIV diagnosis in the country. This will further assist South Africa to achieve global targets such as the United Nation's "HIV 90-90-90" target and the SDGs (especially goal 3).

(c) Enhancement of CC surveillance and oncological facilities among PLWHA on ART.

Further, the ART program in South Africa is the currently largest globally and the recent WHO guidelines recommends ART for all PLWHA irrespective of immunological status (144). We found that the rates and risks of CC increased during the ART era, thus our study provides some evidence for an enhanced CC surveillance system to be urgently put in place to closely monitor the trends and patterns in PLWHA (and indeed in the general population), to further characterise the impact of ART. Increased investment in CC oncological care is necessary since ART may increase the incidence of CC in the nearest future.

(d) Other cervical cancer screening methods and vaccination should be strengthened.

It is further recommended that other screening methods like VIA (or VILI) and HPV DNA typing together, coupled with free vaccination of school girls and boys in their middle childhood, before sexual debut, (primary prevention) should be strengthened since Pap smear screening program appears not to have significantly impacted on the rates of CC in South Africa after more than a decade of its initiation (10,11,22,99). Also, the increased CC rates in young women further supports massive investment in vaccination of young people and South Africa may consider extending the age of vaccination to 26 years (for all it is worth) as recommended by the American College of Obstetricians and Gynaecologists (34). Programs aimed at reducing modifiable risk factors in young people should also be designed.

2. Review of other CC control initiatives and counselling

(a) Holistic review of control of Tobacco usage (including smokeless tobacco)

Since our study linked snuff use and tobacco smoking with CC risk in Black women, it is imperative that current tobacco smoking initiatives should be reviewed to include control of smokeless tobacco. Smokers and snuff users should be informed that their increased risk of CC reverses when they quit the habit.

(b) Public health interventions of vulnerable groups

Focused and enhanced interventions on the identified high risk groups such as Blacks; Coloureds; young women less than 35 years; PLWHA; tobacco smokers and snuff users; women with higher parity and women living in Mpumalanga, North West and Northern Cape provinces is imperative. Furthermore, since the previously reported declining rates in Indians/Asians and Whites appeared to have been stalled, well designed targeted preventive interventions aimed at averting an epidemic of CC among them are necessary.

(c) Cervical cancer monitoring of family planning clients

We recommend that family planning clients on hormonal contraceptives should be closely monitored for CC and they should be counselled that a slight risk exist for extended use of contraceptive after ten years. Also, PLWHA and smokers should be reassured that they do not have extra risk of CC as compared with HIV negative women and non- smokers respectively. These recommendations should be considered in conjunction with other relationships of gynaecological cancers and hormonal contraceptives.

3. Monitoring of relative survival of cervical cancer with the complement mortality to incidence ratio in South Africa

Since the proxy (1-MI:IR) of 5-year survival rate that was utilised in this study was comparable to rates obtained from the use of traditional survival analysis methods, we therefore recommend that this proxy should be further investigated and incorporated as a CC monitoring tool - at least as a stop gap - in South Africa and other LMICs with poor record linkage to inform policy makers on impact of CC control measures (105) .

4. Integration and linkages of cervical cancer prevention into maternal and child health programs and other institutional program and regional cooperation

(a) We recommend that all initiatives of maternal and child health should include CC prevention programs since our study revealed that a considerable proportion of CC patients were women of the reproductive age (59).

(b) Also, CC screening programs should be linked with childhood immunisation programs; markets; banks; religious organisations; hotels and schools/universities so as to target women of the reproductive age groups for screening (59,145).

(c) In addition to the above, cervical cancer screening should be freely discussed and offered to women at appropriate time during ante natal clinics, post-natal clinics and other clinics where married women visit since higher risk was found among them in this study (47).

(d) Also cultural barriers to marriage should be addressed through appropriate social re-engineering since co-habiting couples had higher risk of CC and HIV infections (14)

(e) Our study showed that high rates of CC in South Africa may be related to in-migration from neighbouring countries with poor CC control programs (87). Thus, for South Africa to have a sustained reduction in CC rates, we recommend the country must lead a regional advocacy and collaborative effort to entrench CC control program among the SADC countries (or in the interim among the neighbouring countries).

5.3 Further opportunities for research.

1. The CC rates may have intra provincial variation (23). Therefore, an analysis at the district or local municipality level can be conducted to further characterise the spatial-temporal and intra provincial variation of the risk factors of CC. Such study may clarify the suspicion that sub-districts along the coastal and international boundaries may have higher CC rates. This will aid more focused public health interventions and implementation.

2. A cohort study can be designed by recruiting consenting teenagers that are currently on hormonal contraceptives. They should be vaccinated with HPV vaccine and followed up with regular Pap smear and HIV screen. Such long term longitudinal studies (after critical

review of any ethical concerns) can be used to resolve the current grey areas on CC and hormonal contraceptives especially in young women.

3. Our study found that about a quarter of women with CC died at home. Further research is therefore necessary to investigate the palliative facilities available to CC patients with advanced diseases in the context of contemporary best practice.

4. Future trend analyses (beyond 2009) should assess the impact of the new regulation for mandatory reporting of cancer to the NCR by all laboratories.

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APPENDICES

APPENDIX I

Ethical clearance certificate for the research

R14/49 Dr Olorunfemi Gbenga

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M141163

NAME: (Principal Investigator)	Dr Olorunfemi Gbenga
DEPARTMENT:	School of Public Health
PROJECT TITLE:	Trends and determinants of Incidence and Mortality of Cervical Cancer in South Africa
DATE CONSIDERED:	28/11/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Ntombizodwa Ndlovu and Dr Danuta Kielkowski
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	09/09/2015

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.**

DR G. OLORUNFEMI — 2019/2015

Principal Investigator Signature — Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX II

Plagiarism Report

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 GBENGA OLORUNFEMI (Student number: 971020) am a student registered for the degree of MSc EPIDEMIOLOGY 810 in the academic year 2017

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.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 18/6/17

APPENDIX III

Annual Age standardised mortality Rates of cervical cancer by usual province of Residence in South Africa (2004-2012)

Province/ Year	Western Cape	Eastern Cape	Northern Cape	Free State	KwaZulu-Natal	North West	Gauteng	Mpumalanga	Limpopo
2004	9.3	11.1	23.5	17.1	9.0	8.6	11.7	4.4	13.8
2005	8.4	10.5	20.6	21.4	9.9	11.4	10.4	19.7	12.3
2006	8.6	10.4	18.1	17.1	10.7	9.3	11.5	21.8	10.6
2007	7.9	10.4	15.7	15.8	10.5	11.3	9.7	15.2	12.2
2008	3.7	9.6	15.6	16.9	11.6	12.1	9.1	16.7	12.1
2009	9.0	11.8	174	16.8	11.9	10.4	10.3	20.2	15.0
2010	8.5	12.0	17.5	18.8	11.7	14.3	10.0	19.4	13.8
2011	10.9	9.7	17.2	17.2	13.1	14.8	9.4	20.6	14.9
2012	9.8	8.9	18.0	15.9	14.5	18.5	9.7	19.8	14.8
AAPC(%)	2.3	-1.0	-16.6	-1.3	5.3	8.3	-2.0	1.2	2.8
(95% CI)*	2.1 - 2.5	-1.1 - 0.9	-18.6 - 14.6	-1.4 - 1.2	5.2 5.3	8.1 8.5	-2.09 - 1.99	1.09 1.33	2.7 2.9

* All the AAPC had p-value <0.001

APPENDIX IV

Univariable and multivariable unconditional logistic regression analysis of sensitivity analysis of adding breast cancer to the controls in the sub-study of HIV as the major risk factor of cervical cancer.

	Univariable analysis			Multivariable analysis		
Factor	**COR**	**95% CI**	**P-value**	**AdjOR**	**95% CI**	**P-value**
HIV status						
Negative	1.00	Ref	Ref	1.00	Ref	Ref
Positive	2.00	1.78 - 2.25	<0.001*	2.33	2.04 - 2.67	<0.001*
Missing data	1.75	1.47 - 2.08	<0.001*	1.34	1.10 - 1.63	0.004*
Age						
<50	1.00	Ref	Ref	1.00	Ref	Ref
≥ 50	0.90	0.83 - 0.99	0.03*	0.76	0.68 - 0.86	< 0.001*
Missing data	0.40	0.04 - 3.82	0.42	0.23	0.03 - 1.85	0.166
Ever used Injectable Contraceptives						
Never	1.00	Ref	Ref	1.00	Ref	Ref
yes, <5years	1.08	0.96 - 1.22	0.21	1.19	0.95 - 1.25	0.202
yes, 5-10years	1.26	1.07 - 1.48	0.01*	1.34	1.05 - 1.50	0.013*
yes≥10years	1.06	0.91 - 1.23	0.43	1.17	0.89 - 1.27	0.479
Missing data	0.71	0.54 - 0.94	0.02*	0.97	0.64 - 1.18	0.356
P-value for trend			0.049*			0.262
Ever used Oral contraceptives						
Never	1.00	Ref	Ref	1.00	Ref	Ref
Yes,<5years	0.85	0.75 - 0.97	0.02*	1.09	0.81 - 1.08	0.336
yes,5-10years	0.91	0.75 - 1.10	0.33	1.25	0.84 - 1.27	0.764
yes≥10years	0.71	0.59 - 0.85	<0.001*	1.06	0.73 - 1.08	0.244
Missing data	0.53	0.38 - 0.74	<0.001*	0.86	0.42 - 0.85	0.004*
P-value for trend			*<0.001**			0.035*
Smoking status						
Never	1.00	Ref	Ref	1.00	Ref	Ref
Ex-smoker	1.26	1.06 - 1.50	0.011*	1.25	1.02 - 1.52	0.028*
Current light smoker	1.62	1.39 - 1.88	< 0.001*	1.78	1.50 – 2.11	< 0.001*
Current heavy smoker	1.84	1.23 - 2.76	0.003*	1.94	1.25 – 3.03	0.003*
Missing data	1.43	0.73 - 2.78	0.294	1.10	0.56 – 2.16	0.791
P-value for trend			*<0.001**			<0.001*
Snuff use						
Never	1.00	Ref	Ref	1.00	Ref	Ref
Former users	0.89	0.78 - 1.03	0.108	0.97	0.84 - 1.13	0.729
Current users	1.44	1.28 - 1.63	< 0.001*	1.28	1.12 - 1.45	< 0.001*
Missing data	0.88	0.25 - 3.12	0.841	.80	0.26 - 2.52	0.705
P-value for trend			*<0.001**			0.003*
Lifetime number of sexual partners						
0-1 partner	1.00	Ref	Ref	1.00	Ref	Ref
2-5 partners	1.28	1.12 - 1.47	< 0.001*	1.27	1.10 - 1.47	0.002*
5 and above	1.38	1.16 - 1.65	< 0.001*	1.39	1.14 - 1.70	0.001*
Missing data	0.86	0.64 - 1.15	0.304	0.92	0.67 - 1.26	0.596
P-value for trend			*<0.001**			0.001*
Age at first pregnancy						
≤16yrs	1.00	Ref	Ref	1.00	Ref	Ref
16-21yrs	0.71	0.61 - 0.84	< 0.001*	0.80	0.68 - 0.95	0.009*
21&above	0.50	0.42 - 0.58	< 0.001*	0.59	0.50 - 0.70	< 0.001*
Missing data	0.33	0.27 - 0.42	< 0.001*	0.72	0.48 - 1.06	0.096
P-value for trend			*<0.001**			<0.001*

Table continued

	Univariable analysis			Multivariable analysis		
Factor	**COR**	**95% CI**	**P-value**	**AdjOR**	**95% CI**	**P-value**
Parity						
Nulliparous	1.00	Ref	< 0.001*	1.00	Ref	Ref
1-2	2.98	2.28 - 3.89	< 0.001*	2.96	1.88 - 4.67	< 0.001*
3-4	3.86	2.95 - 5.04	< 0.001*	3.92	2.49 - 6.18	< 0.001*
5 and above	5.40	4.12 - 7.07	< 0.001*	5.42	3.42 - 8.57	< 0.001*
Missing data	7.60	4.77 - 12.10	< 0.001*	5.15	3.13 - 8.47	< 0.001*
P-value for trend			*<0.001**			<0.001*
Educational qualification						
No education	1.00	Ref	Ref	1.00	Ref	Ref
primary school	2.98	1.88 - 4.66	< 0.001*	0.74	0.64 - 0.86	< 0.001*
high school	3.86	2.49 - 6.18	< 0.001*	0.56	0.49 - 0.66	< 0.001*
Tertiary	5.40	3.42 - 8.57	< 0.001*	0.28	0.19 - 0.40	< 0.001*
Missing data	7.60	3.13 - 8.47	< 0.001*	1.67	0.86 - 3.23	0.129
P-value for trend			*<0.001**			<0.001*
Type of residence						
Urban	1.00	Ref	Ref	1.00	Ref	Ref
Rural	2.05	1.82 - 2.32	< 0.001*	1.65	1.44 – 1.88	< 0.001*
Missing data	1.80	0.91 - 3.54	0.091	1.58	0.77 - 3.25	0.212
Year of interview						
1995 – 2000	1.00	Ref	Ref	1.00	Ref	Ref
2001 – 2005	0.45	0.40 - 0.52	< 0.001*	0.49	0.42 - 0.56	< 0.001*
2006 – 2010	0.57	0.51 - 0.63	< 0.001*	0.60	0.54 - 0.69	< 0.001*
P-value for trend			*<0.001**			*<0.001**
Ever had pap smear						
Never	1.00	Ref	Ref			
≥1	0.46	0.40 – 0.52	< 0.001*			
Missing data	0.997	0.905 – 1.10	< 0.951			

Multivariable Model built with: HIV, age ≥50, place of residence (rural/urban), injectable contraceptives; oral contraceptives, time period of diagnosis, number of lifetime sexual partners, age at first pregnancy, current tobacco smoking, snuff use, educational attainment. Pearson's goodness of fit test= 0.0899. COR: crude odd ratio, AdjOR: Adjusted odd ratio. *statistically significant at P-value <0.05

APPENDIX V

Univariable and multivariable unconditional logistic regression analysis of sensitivity analysis of adding breast cancer to the controls in the sub-study of tobacco smoking and alcohol as the major risk factor.

	Univariable unconditional logistic regression analysis			**Multivariable unconditional regression analysis**		
Factors	**COR**	**95% C I**	**P-value**	**Adj OR**	**95% CI**	**P-value**
Smoking status						
Never	1.00	Ref	Ref	1.00	Ref	Ref
Ex-smoker	1.33	1.11 - 1.59	0.002*	1.24	1.12 - 1.66	0.036*
Current light smoker	1.54	1.33 - 1.79	<0.001*	1.69	1.42 - 2.00	<0.001*
Current heavy smoker	1.66	1.12 - 2.47	0.01*	1.73	1.12 - 2.66	0.013*
Missing data	1.50	0.77 - 2.95	0.24	1.04	0.51 - 2.12	0.913
P-value for trend			*<0.001**			<0.001*
Alcohol use						
Non-drinkers	1.00	Ref	Ref	1.00	Ref	Ref
Moderate drinkers	1.54	1.40 - 1.69	<0.001*	0.93	0.81 - 1.07	0.312
Heavy drinkers	1.47	1.22 - 1.78	<0.001*	1.17	0.94 - 1.45	0.169
Missing data	5.15	2.06 - 12.84	<0.001*	2.96	1.15 - 7.63	0.024
P-value for trend			*<0.001**			
Age						
<50	1.00	Ref	Ref	1.00	Ref	Ref
≥ 50	1.15	1.06 - 1.26	0.001*	0.85	0.75 - 0.95	0.006*
Missing data	0.45	0.05 - 4.30	0.49	0.21	0.03 - 1.62	0.136
Snuff use						
Never	1.00	Ref	Ref	1.00	Ref	Ref
Former users	0.96	0.83 - 1.10	0.57	1.03	0.89 - 1.25	0.662
Current users	1.46	1.30 - 1.65	<0.001*	1.25	1.10 - 1.43	0.001*
Missing data	0.76	0.22 - 2.58	0.66	0.55	0.18 - 1.61	0.277
P-value for trend			*<0.001**			0.003
Parity						
Nulliparous	1.00	Ref	Ref	1.00	Ref	Ref
1-2	2.98	2.29 - 3.89	< 0.001*	3.05	1.95 - 4.79	< 0.001*
3-4	4.33	3.32 - 5.65	< 0.001*	4.30	2.73 - 6.77	< 0.001*
5 and above	6.32	4.83 - 8.28	< 0.001*	5.66	3.58 - 8.97	< 0.001*
Missing data	8.10	5.09 - 12.90	< 0.001*	5.39	3.30 - 8.81	< 0.001*
P-value for trend			*<0.001**			<0.001*
Lifetime number of sexual partners						
0-1 partner	1.00	Ref	Ref	1.00	Ref	Ref
2-5 partners	1.17	1.02 - 1.35	0.021*	1.25	1.07 - 1.45	0.004*
5 and above	1.11	0.93 - 1.32	0.259	1.26	1.03 - 1.55	0.023*
Missing data	0.80	0.60 - 1.08	0.141	0.91	0.66 - 1.26	0.574
P-value for trend			0.258			0.001*

Table continued

	Univariable analysis		Multivariable analysis			
Factor	**COR**	**95% CI**	**P-value**	**AdjOR**	**95% CI**	**P-value**
Marital status						
Single/Never Married	1.00	Ref	Ref	1.00	Ref	Ref
Married/Living together	1.24	1.10 - 1.40	< 0.001*	1.20	1.05 - 1.38	0.007*
Widowed	1.36	1.18 - 1.56	< 0.001*	1.08	0.92 - 1.28	0.334
Separated	1.16	0.997 - 1.36	0.055	1.20	1.01 - 1.43	0.037*
Missing data	1.22	0.50 - 2.97	0.656	0.73	0.24 - 2.24	0.585
Educational qualification						
No education	1.00	Ref	Ref	1.00	Ref	Ref
primary school	0.69	0.60 - 0.79	< 0.001*	0.74	0.64 - 0.86	< 0.001*
high school	0.40	0.35 - 0.46	< 0.001*	0.54	0.47 - 0.63	< 0.001*
Tertiary	0.15	0.11 - 0.21	< 0.001*	0.29	0.20 - 0.41	< 0.001*
Missing data	1.97	0.95 - 4.08	0.068	2.22	1.02 - 4.80	0.043
P-value for trend			*<0.001**			<0.001*
Age at first pregnancy						
≤16yrs	1.00	Ref	Ref	1.00	Ref	Ref
16-21yrs	0.75	0.65 - 0.88	< 0.001*	0.83	0.70 - 0.98	0.025*
21&above	0.54	0.47 - 0.64	< 0.001*	0.62	0.53 - 0.74	< 0.001*
Missing data	0.34	0.27 - 0.42	< 0.001*	0.76	0.51 - 1.12	0.162
P-value for trend			*<0.001**			<0.001*
Type of residence						
Urban	1.00	Ref	Ref	1.00	Ref	Ref
Rural	2.18	1.93 - 2.46	< 0.001*	1.66	1.45 - 1.90	< 0.001*
Missing data	1.50	0.78 - 2.85	0.223	1.27	0.62 - 2.61	0.513
HIV status						
Negative	1.00	Ref	Ref	1.00	Ref	Ref
Positive	1.08	0.97 - 1.20	< 0.001*	1.40	1.23 - 1.58	0.153
Missing data	1.70	1.42 - 2.02	0.153	1.44	1.18 - 1.76	<0.001
Ever had pap smear						
Never	1.00	Ref	Ref			
≥1	0.48	0.42 - 0.55	< 0.001*			
Missing data	1.07	0.97 - 1.17	0.198			
Year of interview						
1995 – 2000	1.00	Ref	Ref	1.00	Ref	Ref
2001 – 2005	0.44	0.39 - 0.50	< 0.001*	0.46	0.39 - 0.55	< 0.001*
2006 – 2010	0.53	0.48 - 0.59	< 0.001*	0.57	0.48 - 0.67	< 0.001*
P-value for trend			*<0.001**			<0.001*

Multivariate Model built with: HIV, age ≥50, place of residence (rural/urban), injectable contraceptives; oral contraceptives, time period of diagnosis, number of lifetime sexual partners, age at first pregnancy, current tobacco smoking, snuff use, educational attainment. COR: crude odd ratio, AdjOR: Adjusted odd ratio *statistically significant at P-value <0.05

APPENDIX VI

Univariable and multivariable unconditional logistic regression analysis of sensitivity analysis of adding breast cancer to the controls in the sub-study of reproductive and hormonal factors as the major risk factor.

	Univariable analysis			Multivariable analysis		
Factor	**COR**	**95% CI**	**P-value**	**Adj OR**	**95% CI**	**P-value**
Age						
<50	1.00	Ref	Ref	1.00	Ref	Ref
≥ 50	0.92	0.8 - 1.00	0.04*	0.77	0.69 - 0.86	<0.001*
Missing data	0.51	0.05 - 4.88	0.56	0.29	0.03 - 2.89	0.294
Educational qualification						
No education	1.00	Ref	Ref	1.00	Ref	Ref
primary school	0.72	0.63 - 0.81	0.001*	0.73	0.64 - 0.83	<0.001*
high school	0.50	0.45 - 0.57	0.001*	0.57	0.50 - 0.66	<0.001*
Tertiary	0.19	0.13 - 0.26	0.001*	0.29	0.19 - 0.40	<0.001*
Missing data	1.32	0.75 - 2.31	0.34	1.41	0.76 - 2.61	0.270
P-value for trend			*<0.001**			<0.001*
Type of residence						
Urban	1.00	Ref	Ref	1.00	Ref	Ref
Rural	1.78	1.59 - 1.99	<0.001*	1.43	1.26 - 1.62	< 0.001*
Missing data	1.02	0.58 - 1.79	0.96	0.97	0.53 - 1.77	0.910
Marital status						
Single/Never Married	1.00	Ref	Ref	1.00	Ref	Ref
Married/Living together	1.18	1.06 - 1.33	0.003*	1.13	0.998 - 1.291	0.054
Widowed	1.16	1.02 - 1.33	0.02*	1.01	0.86 - 1.18	0.874
Separated	1.14	0.98 - 1.32	0.09	1.13	0.96 - 1.34	0.131
Missing data	1.25	0.53 - 2.95	0.61	1.09	0.42 - 2.85	0.862
Age at first pregnancy						
≤16yrs	1.00	Ref	Ref	1.00	Ref	Ref
16-21yrs	0.69	0.60 - 0.80	<0.001*	0.74	0.63 - 0.86	<0.001*
21&above	0.49	0.43 - 0.57	<0.001*	0.55	0.47 - 0.64	<0.001*
Missing data	0.32	0.26 - 0.40	<0.001*	0.71	0.50 - 1.01	0.059
P-value for trend			*<0.001**			<0.001*
Parity						
Nulliparous	1.00	Ref	Ref	1.00	Ref	Ref
1-2	3.18	2.45 - 4.13	<0.001*	3.19	2.10 - 4.83	<0.001*
3-4	4.13	3.18 - 5.36	<0.001*	4.08	2.68 - 6.21	<0.001*
5 and above	5.38	4.14 - 7.00	<0.001*	5.28	3.46 - 8.07	<0.001*
Missing data	13.39	8.17 - 21.95	<0.001	12.21	7.49 - 19.90	<0.001
P-value for trend			*<0.001**			<0.001*
Lifetime number of sexual partners						
0-1 partner	1.00	Ref	Ref	1.00	Ref	Ref
2-5 partners	1.33	1.17 - 1.51	<0.001*	1.34	1.16 - 1.54	<0.001*
5 and above	1.38	1.16 - 1.63	<0.001*	1.43	1.19 - 1.73	0.001*
Missing data	0.73	0.55 - 0.96	0.02	0.78	0.58 - 1.05	0.095
P-value for trend			*<0.001**			<0.001*

Ever used oral Contraceptives						
Never	1.00	Ref	Ref	1.00	Ref	Ref
yes, <5years	0.93	0.82 - 1.06	0.29	1.01	0.88 - 1.15	0.915
yes,5-10years	0.88	0.73 - 1.06	0.18	0.96	0.79 - 1.17	0.702
yes≥10years	0.81	0.68 - 0.97	0.02*	0.96	0.79 - 1.17	0.711
Missing data	0.53	0.39 - 0.73	<0.001	0.62	0.44 - 0.87	0.006
P-value for trend			*0.008**			
Ever used Injectable						
Never	1.00	Ref	Ref	1.00	Ref	Ref
yes, <5years	1.07	0.95 - 1.20	0.27	1.03	0.91 - 1.18	0.551
yes,5-10years	1.15	0.99 - 1.34	0.06*	1.14	0.97 - 1.34	0.122
yes≥10years	1.16	1.01 - 1.34	0.04*	1.11	0.94 - 1.31	0.210
Missing data	0.62	0.47 - 0.81	<0.001	0.73	0.55 - 0.97	0.031
P-value for trend			*0.009**			
Smoking status						
Never	1.00	Ref	Ref	1.00	Ref	Ref
Ex-smoker	0.99	0.84 – 1.16	0.856	0.94	0.79 - 1.13	0.514
Current light smoker	1.26	1.10 – 1.44	0.001*	1.34	1.15 - 1.56	< 0.001*
Current heavy smoker	0.87	0.63 – 1.20	0.398	0.87	0.61 - 1.24	0.439
Missing data	1.05	0.58 – 1.90	0.881	0.96	0.53 - 1.75	0.888
P-value for trend			*0.004**			*0.002**
Snuff use						
Never	1.00	Ref	Ref	1.00	Ref	Ref
Former users	0.91	0.80 – 1.04	0.173	0.94	0.82 - 1.08	0.381
Current users	1.68	1.50 – 1.87	< 0.001*	1.48	1.31 - 1.68	< 0.001*
Missing data	0.86	0.26 – 2.85	0.800	0.69	0.20 - 2.35	0.554
P-value for trend			< 0.001*			0.003*
HIV status						
Negative	1.00	Ref	Ref	1.00	Ref	Ref
Positive	1.53	1.38 - 1.70	< 0.001*	1.74	1.54 - 1.96	< 0.001*
Missing data	1.77	1.50 - 2.08	< 0.001	1.56	1.31 - 1.87	< 0.001
Year of interview						
1995 – 2000	1.00	Ref	Ref	1.00	Ref	Ref
2001 – 2005	0.51	0.45 - 0.58	< 0.001*	0.55	0.48 - 0.62	< 0.001*
2006 – 2010	0.69	0.62 - 0.76	< 0.001*	0.73	0.65 - 0.82	< 0.001*
P-value for trend			*<0.001**			<0.001*
Ever had pap smear						
Never	1.00	Ref	Ref			
≥1	0.48	0.42 - 0.55	<0.001*			
Missing data	0.87	0.79 - 0.95	0.002			

Hosmer-Lemeshow Chi2 (8) = 11.3, P-value = 0.19. Multivariable Model built with: HIV, Age ≥50, Place of residence (rural), Injectable contraceptives; oral contraceptive, time period of diagnosis, age at first pregnancy, parity, marital status, tobacco smoking, snuff use, educational attainment and sexual partnership. COR: crude odds ratio, AdjOR: Adjusted odds ratio. COR: Crude Odds ratio. *statistically significant at P-value <0.05