Tampere University

NONTUTHUZELO IRIS MURIEL SOMDYALA

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Understanding the Incidence of this Disease and Building Infrastructure towards Intervention

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ACADEMIC DISSERTATION
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DEDICATION

To the Almighty, the God Father, for blessing me with purposeful life, including attaining this highest education level; the Ph.D.

The guiding living spirits of my parents; late Mr. France Cromwell Dada & Mrs. Nobantu Fanny Dada, for providing and raising me in a conducive environment

My late husband, Mr. Siphelele Henry Somdyala, for looking beyond the woman in me and seeing a potential citizen with a purpose in the economy of our beloved country South Africa

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Last but not least, my dear sons (Khayalethu, Thandolwethu, Msuthu & Thulasizwe) and only daughter (Siphokazi) took it easy and survived many times of being away while studying. I couldn't fulfill the full parental role.

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ABSTRACT

Non-communicable diseases (NCDs) currently in low-middle-income countries (LMICs) account for 40% of the total burden of disease. They are recognized as a significant threat to health and the economy. Cancer is among NCDs challenging the LMICs today with projected trends that are continuously increasing. Cervical cancer is estimated as the fourth cause of global incidence and mortality. Women experience high incidence and mortality rates due to this cancer in LMICs, with the highest burden borne by countries in Sub-Saharan Africa (SSA). The problem of cervical cancer was elevated to a severe level of the SSA region by the onset of the Human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). In addition, many women are unscreened or under-screened because there are no organized screening programs for the early detection of pre-cancerous lesions.

South Africa is the only country in the SSA region that offers the national cytology-based screening. Yet, cervical cancer is ranked the second most common cancer and cause of death among women and 8th of the top 10 contributors to Disability Adjusted Life Years (DALYs). Poor screening performance is one of the reasons for the high invasive cervical cancer, which remains a health challenge. Given South Africa's disparate distribution of public healthcare resources, it is essential to know whether the mass population-based cytology screening program is available to the rural population of the Eastern Cape Province of South Africa. This research aims to understand the burden of cervical cancer in this population. The objectives include describing the incidence of cervical cancer, investigating geographical differences, assessing screening coverage, and examining the survival rate using collaborative studies results in the region and internationally to develop an appropriate intervention program.

Using a population-based cancer registry, an observational study, Study I, reported cervical cancer as the most common cancer in women, consistently and progressively increasing in the rural population of the Eastern Cape Province. This Study also investigated trends in the age-standardized and age-specific incidence rates of cervical cancer in two distinct geographic areas, the southern and northern covered by the cancer registry. Results identified distinct differences in these two areas. In relation to the overall age-standardised incidence rates (ASRs) per 100,000 women were 22.0 (95% CI:20.0-24.0) in 1998-2002, 24.4 (95% CI:22.4-26.4) in 2003-2007 and 29.2 (95% CI:27.3-31.6) in 2008-2012. While the ASRs in the entire region showed a progressive

increase, the southern area slightly decreased over the same period. They were 20.0 (95% CI:18.5-21.4) in 1998-2002, 19.1 (95% CI:16.5-21.7) in 2003-2007 and 18.8 (95% CI:16.2-23.4) in 2008-2012. In contrast, the ASRs in the northern area increased significantly from 24.0 (95% CI: 21.1-27.0) in 1998-2002, to 29.7 (95% CI: 26.6%-32.8%) in 2003-2007 and 39.0 (95% CI: 35.6-42.5) in the period 2008-2012.

Study II described cervical cancer screening program trends based on routinely collected health service data for women 30 years and older reported by health sub-district and year. It is important to note that these service health data were only included in the routine information systems from 2007, with deficient coverage in the northern area at 2.2% in 2007 and 4.3% in 2008. A steady increase was observed from 2009 to 2012 to only 14.8% in 2012. The southern area, which spans two health sub-districts, Mbhashe and Mnquma, reported slightly better coverage of the screening program, with an average of 7.7% in 2007. There was an increase to 41.0% in 2012, with an anomalous coverage of 69.0% reported for the Mbhashe sub-district in 2010. Furthermore, this sub-district had almost twice the screening percentage of the Mnquma sub-district (52.3% vs. 29.7%) in 2012.

LMICs struggle to generate historical cancer incidence data over a period due to little investment committed to sustaining this critical infrastructure needed for cancer control in these countries. There are also many competing health demands in SSA that cripple the establishment and maintenance of PBCRs, the source of these historical cancer incidence data. Hence, notably in SSA, only a few cancer incidence data are reported. Despite the challenges, SSA faces in cancer registration compared to other LMICs, directed investment towards staff training and infrastructure limitations can improve the current situation. These critical areas need international investment, including the member states, to sustain and support cancer registration. The Eastern Cape Province PBCR is among the few SSA registries that survived those challenges and reports data on cancer incidence of a rural population. This research highlights the importance of cancer registration which tracked the high cervical cancer incidence experienced by women in the rural Eastern Cape Province that progressively increased over time. Important suggesting pointers of the low or non-existence of screening in this population include low survival to this cancer due to an advanced stage at diagnosis that many women present with, showing that clinical signs and symptoms made diagnosis rather than prompt screening. This information significantly impacts decision-making and a statistical infrastructure for health information. It is also essential to inform the national government about a more targeted control program to reduce cervical cancer burden, improve survival, and review the current cytology-based screening program policy rolled out more than 20 years ago in South Africa.

TIIVISTELMÄ

Tarttumattomat sairaudet eli kansantaudit kattavat noin 40% tautitaakasta pieni- ja keskituloisissa maissa ja näiden sairauksien taakka kasvaa jatkuvasti. Kohdunkaulan syöpä on koko maailmassa ilmaantuvuudeltaan ja kuolleisuudeltaan naisten neljänneksi yleisin syöpä. Kohdunkaulan syöpä koskettaa erityisesti pieni- ja keskituloisia maita, joista Saharan eteläpuoleinen Afrikka on korkeimman ilmaantuvuuden alueita. Alueella on muitakin haasteita, kuten HIV-infektion leviäminen ja toimivan kohdunkaulasyövän seulontaohjelman puuttuminen.

Etelä-Afrikka on ainoa maa Saharan eteläpuoleisessa Afrikassa, jossa naisilla on kansallisesti mahdollisuus hakeutua maksuttomaan kohdunkaulan irtosolutestiin (ns. Papa-testi) syövän esiasteiden ja varhaisen toteamisen mahdollistamiseksi. Tästä huolimatta kohdunkaulasyöpä on toiseksi yleisin syöpä ilmaantuvuudeltaan ja kuolleisuudeltaan ja vaikuttaa merkittävästi myös laatupainotettujen elinvuosien menetykseen. Irtosolutestiin perustuvan seulonnan huono toimivuus on yksi syy kohdunkaulasyövän korkeaan ilmaantuvuuteen.

Väitöstutkimuksella haluttiin selvittää, onko väestön irtosolutestiin perustuva seulonta toimiva itäisen provinssin (Eastern Cape Province) alueen maaseutuväestössä. Tutkimuksella selvitettiin myös alueen kohdunkaulasyövän aiheuttama tautitaakka ilmaantuvuuden alueellisten erojen, seulonnan kattavuuden ja potilaiden elossaololukujen valossa. Tavoitteena on voida kehittää toimiva kohdunkaulasyövän ehkäisyohjelma.

Itäisen provinssin väestöpohjaisen syöpärekisterin tietojen avulla tutkittiin kohdunkaulasyövän ilmaantuvuutta ja sen muutoksia kahdella maantieteellisellä alueella, eteläisellä ja pohjoisella. Vaikka koko itäisen provinssin alueella nähtiin kohdunkaulasyövän ikävakioidun ilmaantuvuuden selkeä ja jatkuva kasvu vuosista 1998-2002 vuosiin 2008-2012, eteläisellä osa-alueella ilmaantuvuus pysyi lähes ennallaan (arvosta 20/100 000 arvoon 19/100 000) ja pohjoisella osa-alueella se kasvoi merkittävästi (arvosta 24/100 000 arvoon 39/100 000).

Kohdunkaulasyövän seulontaa kuvaamaan raportoitiin irtosolutestissä käyneiden 30-vuotiaiden tai sitä vanhempien naisten osuus kalenterivuoden ja alueen mukaisissa ositteissa. Testausta koskevat tiedot saatiin terveyspalveluiden käytön rutiiniseurantajärjestelmästä vuodesta 2007 alkaen. Irtosolutestauksessa käyneiden naisten osuus kaikista alueen 30-vuotta täyttäneistä naisista oli tietojen perusteella

vähäinen pohjoisella alueella vuosina 2007-2009 ja saavutti vajaat 15% vuoteen 2012 mennessä. Eteläisen alueen kaksi terveysaluetta, Mbhashe ja Mnquma raportoivat selkeästi korkeamman seulonnan kattavuuden, vajaa 8% vuonna 2007 mutta jo 41% vuonna 2012.

Itäisen provinssin väestölähtöinen syöpärekisteri on niitä harvoja Saharan eteläpuoleisen Afrikan rekistereitä, jotka ovat pystyneet raportoimaan syöpäilmaantuvuutta maaseutuväestössä. Väitöstutkimus korostaa syövän rekisteröinnin tärkeyttä naisten syöpätaakan seurannassa. Koska olemassa oleva irtosolutestaus on alueella vähäistä eikä toimi optimaalisesti, ovat kohdunkaulan syövät todettaessa usein levinneitä. Tämä puolestaan johtaa huonoon ennusteeseen. Tutkimuksella pyrittiin tuottamaan tietoa päätöksentekoa varten. On tärkeää tiedottaa kansallisia tahoja kohdunkaulasyövän taakan jatkuvasta kasvusta, jotta sen ehkäisyyn voidaan panostaa. Kohdunkaulasyövän ilmaantuvuus- ja kuolleisuusluvut ovat kasvaneet irtosolutestin tarjonnasta huolimatta. Nykyinen maksuton irtosolutestitoiminta, joka on käynnistetty jo yli 20 vuotta sitten Etelä-Afrikassa, tulee uudistaa.

CONTENTS

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ABBREVIATIONS

AFCRN	African Cancer Registry Network
AIDS	Acquired Immunodeficiency Syndrome
ASCUS	Atypical squamous of undermined significance
ASR	Age-standardized Incidence Rates
BoDRU	Burden of Disease Research Unit
CANSA	Cancer Association of South Africa
CC	Cervical cancer
CI	Confidence Interval
CIN	Cervical intraepithelial neoplasia
COPD	Chronic Obstructive Pulmonary Diseases
CVD	Cardiovascular Diseases
DALYs	Disability Adjusted Life Years
DHIS	District Health Information System
DNA	Deoxyribonucleic acid
DOAJ	Directory of Open Access Journal
EC	Eastern Cape
ECCR	Eastern Cape Cancer Registry
GBD	Global Burden of Disease
GICR	Global Initiative for Cancer Registry
HICs	High-Income Countries
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HR	High Risk
HSIL	High grade squamous intraepithelial lesions
IARC	International Agency for Research on Cancer
ICCs	Invasive cervical cancers
ICD-O	International Coding of Diseases for Oncology
KS	Kaposi sarcoma
LEEP	Loop electrosurgical excision procedure
LMIC	Low-middle-income countries

LSA	Local service area
LSILS	Low grade squamous intraepithelial lesions
NCD	Non-communicable Diseases
NHLS	National Health Laboratory Services
OC	Oesophageal cancer
OR	Odds Ratio
PBCR	Population-based Cancer Registry
PBCRs	Population-based Cancer Registries
PSA	Protein specific antigen
RR	Relative Risk
SAMRC	South African Medical Research Council
SILS	Squamous intraepithelial lesions
SRR	Standardized Rate Ratio
SSA	Sub-Saharan Africa
StatsSA	Statistics South Africa
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
UTA	University of Tampere
VIA	Visual inspection with acetic acid
VILI	Visual inspection with Lugol's iodine
WHA	World Health Assembly
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

The original articles listed in Roman numerals; I to III below are the basis of this dissertation. They were also used as references in the text. In addition to the original articles' material, some previously unpublished data are also presented in this doctoral thesis.

I Somdyala, NIM., Bradshaw, D., Gelderblom, WCA., Parkin, DM. (2010). Cancer incidence in a rural population of South Africa, 1998–2002. Int. J. Cancer: 127, 2420–2429. DOI: 10.1002/ijc.25246

II Somdyala, NI., Parkin, DM., Sithole, N., Bradshaw, D. (2014). Trends in cancer incidence in rural Eastern Cape Province, South Africa, 1998–2012. Int. J. Cancer: 136, E470-E474. DOI: 10.1002/ijc.29224

III Somdyala, NIM., Bradshaw, D., Dhansay, MA., Stefan, DC. (2020). Increasing cervical cancer incidence in rural Eastern Cape Province of South Africa from 1998 to 2012: A population-based cancer registry study. JCO Global Oncol 6:1–8

1 INTRODUCTION

For the past three decades, global health has faced challenges of non-communicable diseases (NCDs) and communicable diseases (Boutayeb & Boutayeb, 2005; Bygbjerg, 2012; Pillay-van Wyk et al., 2016; Shao & Williamson, 2012). The worst other health challenge experienced by the low-income countries (LMICs), particularly those in Africa was the Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) (Gona et al., 2020). To this pandemic, the global health sector invested highly towards lessening its impact, and an approximate amount of $562·6 billion was spent. Of this expenditure, global health spent 57.6% on HIV/AIDS prevention, treatment, and care between 2000 and 2015 (Dieleman, 2019). These estimates on HIV/AIDS spending are crucial to know as they impact priorities to consider in the fiscal budget by LMICs. On the other hand, there has been significant improvement in communicable diseases management and increased life expectancy and risk of NCDs in these countries (Beaglehole & Yach, 2003; Vineis & Wild, 2014). As the disease epidemiology changes, health systems are usually unprepared to face this double disease burden putting a heavy-duty on households expected to budget out of pocket (Bollyky, Templin, Cohen, & Dieleman, 2017). Since 2011 global politics has shown commitment to reducing the burden of NCDs through the adoption of the Sustainable Development Goals and the World Health Organization (WHO) Global Action Plan on Non-Communicable Diseases (Fitzmaurice et al., 2018; UNAIDS, 2015; WHO, 2011, 2017).

1.1 Non-communicable diseases (NCDs) and cancer in Africa: Why are they becoming a public health concern

Globally, the increased NCDs burden threatens health, economies, and societies (Abegunde, Mathers, Adam, Ortegon, & Strong, 2007; Beaglehole et al., 2011; Beaglehole & Yach, 2003; Islam et al., 2014; Mathers & Loncar, 2006; WHO, 2011). NCDs are defined as insidious medical conditions and, unlike communicable diseases, not passed on from one affected person to others. Modifiable risk factors and environmental factors directly cause NCDs (Kim & Oh, 2013). There is also a genetic

predisposition associated with NCDs. Those of global concern are five including recently (i) Mental Health, (ii) cardiovascular diseases (CVD) are grouped as heart and blood vessels disorders (Biglu, Ghavami, & Biglu, 2016), (iii) cancers are a mix of different kinds of diseases caused either by infections, lifestyle or environmental factors (Vineis & Wild, 2014), (iv) diabetes a chronic metabolic disorder that has increased, particularly Type 2 all over the world. In some countries, it is considered an epidemic (Olokoba, Obateru, & Olokoba, 2012), and (v) chronic obstructive pulmonary disease (COPD) is a chronic obstructed airflow disease of the lungs resulting in burdened breathing. It mainly cannot be reversed (WHO, 2011).

In most high-income countries (HICs), several studies observed a decline in NCDs since the 1960s (Backholer et al., 2011; Stringhini et al., 2012; Unal, Critchley, & Capewell, 2004). This decline is attributed to the decrease in population levels of significant risk factors (Backholer et al., 2011; Reddy, 2002; WHO, 2011) and an improvement in treatment (Backholer et al., 2011; Stringhini et al., 2012). Conversely, while in LMICs, life expectancy has improved because of better managed communicable diseases, globalization of economies and behaviours in these countries increased the risk of NCDs, doubling the disease burden (Beaglehole & Yach, 2003; Vineis & Wild, 2014). NCDs' total disease burden in LMICs is currently 40%, of which 86% are premature deaths with gross economic losses estimated up to US$7 trillion over the next 15 years (Abegunde et al., 2007; Beaglehole & Yach, 2003; WHO, 2018). From these figures, millions of people can get trapped in poverty in these communities (Alwan & Maclean, 2009; Kulik, 2013; Reddy, 2002; Schmidt et al., 2011; WHO, 2011). Trends predict that NCDs will account for more than five times the estimated deaths by 2030 compared to communicable diseases in the continent of Africa, with similar impact measures on both men and women (WHO, 2011).

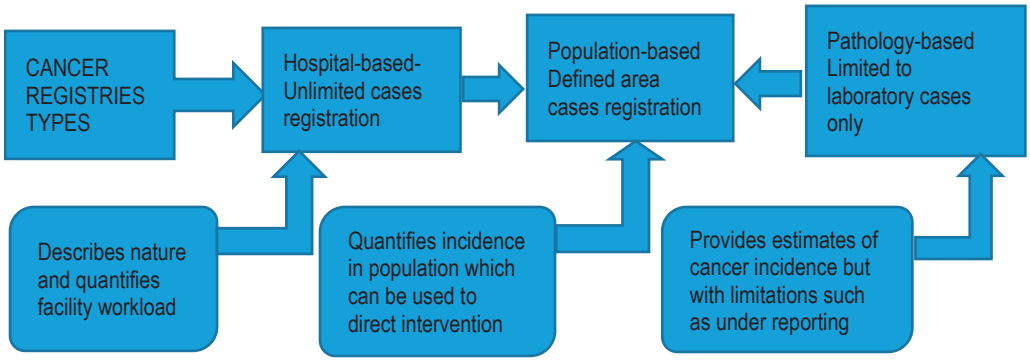
In South Africa, (Nojilana et al., 2016) observed that NCDs already contributed to 39% of premature deaths and are the top cause of mortality. This scenario threatens the country's development and increases the socio-economic pressures the government must deal with. While also shows the multi-layered failure in governance systems, particularly in healthcare policy implementation and regulation. In 2011, NCDs were high on the development agenda during the WHO Independent High-level Commission. Subsequently, the WHO Global Action Plan for the Prevention and Control of NCDs (2013 to 2020) and the United Nations Sustainable Development Goals 2030 realized the need to reduce premature mortality from NCDs by one-third in 2030 (Bennett et al., 2020; WHO, 2013, 2019). As a matter of priority, well-structured data are needed to inform the kind of actions for the identified target group.

1.2 Cancer registries: Usefulness and their role in cancer epidemiology

Systematic cancer surveillance plays a key role in evidence-based cancer control studies that reduce cancer incidence, morbidity, and mortality (Parkin, 2008). Cancer surveillance is well established in HICs, while LMICs still meet many hurdles. However, there is an attempt in Africa made by a few population-based cancer registries. These registries collect and generate internationally acceptable cancer data (Parkin et al., 2008). Quality and accuracy of data provided by these registries are essential in decision making; hence most of them are established in urban areas where there are better medical centres and well-established sources for better diagnosis of sites and case finding (Bray & Ferlay, 2014; Parkin et al., 2008). In Africa, better cancer estimates play a pivotal role in cancer control efforts and evaluation thereof. They are also crucial to the health planning authorities when prioritizing those efforts to reduce the burden and suffering from cancer in their respective communities.

Cancer surveillance forms the foundation and infrastructure that supports cancer control plans, including setting up and monitoring the success of the national cancer control programs, conducting studies that look at the cause and effects of cancer, and providing information on stage distribution, treatment patterns, and survival (Parkin, 2008). Cancer registration is constituted by various data collection activities of which primary sources are three types of cancer registries (Parkin, 2008). Below is an illustration of these cancer registry types summarised, differences, and usefulness highlighted (Figure 1).

Figure 1. Types of cancer registries



A hospital-based cancer registry is a primary source for the population-based cancer registry (PBCR). In contrast, the pathology-based registry is helpful in case linkage, thereby improving the quality and accuracy of diagnoses (Powel & Young, 1991). Documentation of all cases in these registries contributes to a generation of best estimates of cancer burden in a defined area covered by the PBCR. The main goal of a PBCR is to systematically and continuously collect information on each new incident of cancer cases in a defined population, keep and update this information, analyze periodically to estimate the incidence of that population at risk (Parkin, 2008). PBCRs provide unbiased cancer incidence rates and statistics for comparing cancer risk between populations (Parkin, 2008). They are designed as an essential element to support national cancer control programs. National cancer control programs are some of the cancer control strategies that benefit from cancer registration, including evaluating the effectiveness of those programs that include cytology screening for cervical cancer (Piñeros, Znaor, Mery, & Bray, 2017).

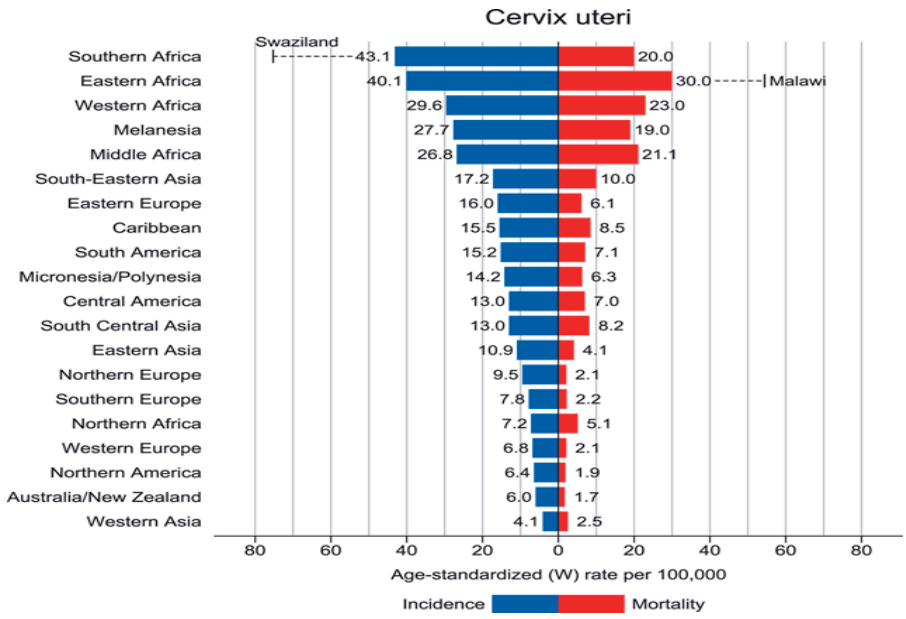
Population-based cancer registration in SSA covers only 14% of the total population, of which only 1% of the population meets the international set standards. It is included in the global cancer incidence publication, the Cancer Incidence in Five Continents (CI5). At the same time, the remaining 13% population is still struggling to meet the criteria for inclusion (Parkin, 2008). The International Agency for Research on Cancer (IARC) of the WHO in 2012 started a process that sought to address shortcomings in data generation of good quality incidence data, especially in LMICs (IARC, 2012). IARC is n partnership with other cancer organizations. It is hoped that Global Initiative for Cancer Registry (GICR) Development and African Cancer Registry Network (AFCRN) can help to substantially improve the generation and availability of quality cancer data even in SSA, where currently is scarce.

Africa still experiences cancer registration challenges compared to developed countries. However, better cancer registration can still be achieved if the investment is directed towards training staff, addressing infrastructure challenges, and dedicated funding to support cancer registry activities and sustainability. Uganda, Zimbabwe for many years, and recently Kenya, Malawi, Seychelles, and South Africa have successfully generated cancer incidence that met the international standard criteria (Bray et al., 2015; Forman et al., 2013). These registries' results are a statistical infrastructure for health information, particularly cancer in these countries. They are essential in informing health planning authorities about incidence, survival, and the impact of cancer control and intervention programs.

1.3 Cervical cancer incidence in sub–Saharan Africa

Cancer is among NCDs that are challenging the world's public health today. The global cancer burden shift and projected trends continuously increasing in poor populations of LMICs are of great concern as these countries have the least ability to cope despite being hit the hardest. Global estimates predict that the lifetime risk of developing cancer is 1 in 8 for men and 1 in 10 for women (Bray et al., 2018). Globally, cervical cancer accounts for 6% of females and is ranked as the fourth most common cancer and cause of death (Bray et al., 2018). Figure 2 shows the region-specific incidence and mortality age-standardized rates (ASR) for cervical cancers in 2018. Global estimations of new cases are 570 000, of which 311 000 (54.5%) are deaths. Of these deaths, women in LMICs account for 90%, with the highest burden experienced by countries in SSA (Bray et al., 2018) (Figure 2).

Figure 2. Global age-standardized incidence and mortality rates for cervical cancers in 2018, by region. Rates are shown in descending order of the world (W) age-standardized rate, and the highest national age-standardized rates for incidence and mortality are superimposed



Source:(Bray et al., 2018)

For several decades, relatively well-controlled cervical cancer in HICs has resulted from good population-based cervical screening programs and effective cancer treatment services. Hence, we see rates of incidence that are 7 to 10 times lower in these countries,

such as North America, Australia/New Zealand, and Western Asia (Saudi Arabia and Iraq) (Bray et al., 2018). However, in SSA, the risk of developing cervical cancer is high, with an ASR of 43.1 per 100 000 population. These high incidence rates are observed in Southern Africa; for example, ESwatini, formerly known as Swaziland, has the highest incidence rates globally. The risk of dying due to this cancer is almost double that in developed countries with an ASR of 20.0 per 100 000 (Bray et al., 2018; Parkin, 2008). Eastern Africa (Malawi and Zimbabwe) with the highest mortality rates, and Western Africa (Guinea, Burkina Faso, and Mali) (Bray et al., 2018). Late diagnosis and inadequate cancer management result from limited or no access, either financially or geographically, or both. These are also the leading causes of these high mortality rates in Africa (Chokunonga et al., 2004). Women in SSA lose more years to cervical cancer than to any other type of cancer. Unfortunately, these women are affected at their critical time of life with a negative stability impact on their families both socially and economically (Anorlu, 2008). Women living in SSA have a high risk of developing cervical cancer. About 70% of these women live in rural areas with limited access or sometimes no screening in their lifetime and poor treatment services (Parkin et al., 2008).

In South Africa, cervical cancer is ranked the second most common cancer and cause of death among women. It is ranked 8th out of the top ten contributors to Disability Adjusted Life Years (DALYs) (Dicker, Nguyen, Abate, Abate, & Murray, 2018). It is more common in black African women than other ethnic groups in South Africa, with rates between 26.6 and 29.1 per 100 000 women (NCRSA, 2012). Worryingly, even higher ASRs from 18.8 to 39.0 per 100,000 women were reported in the population living in a defined rural region of the Eastern Cape Province covered by the Eastern Cape Cancer Registry (ECCR) (Somdyala, Bradshaw, Dhansay, & Stefan, 2020; Somdyala, Parkin, Sithole, & Bradshaw, 2015). The relative survival to this cancer is also low; just above 60% in the first year, but drops below 50% in both 3 and 5 years compared to other high middle-income countries such as Mauritius (Allemani et al., 2018; Allemani et al., 2015; Sengayi-Muchengeti et al., 2020). One of the contributing factors to the poor survival of this disease is late presentation, most often at an advanced stage.

Over time, these incidence rates in South Africa are unacceptably high because this country has a national cytology-based screening program. Several factors based on health care and health systems infrastructure, socio-economic status, culture, and access to facilities and information are associated with these increasing trends (Mary Kawonga & Sharon Fonn, 2008; Michelow & Dubb, 2003; Moodley, 2006; Smith, Moodley, & Hoffman, 2003). The vicious cycle of poverty is more visible in rural areas than urban areas, which results in higher numbers in these communities. The level of understanding

due to poor, low, and limited schooling standards predisposes these women not to understand the importance of preventative behavior – including accessing screening. The absence of, or limited access to, information about cervical cancer prevention and early diagnosis through screening is a significant factor that leads to these unfortunate numbers, and similarly, a concern.

Also, in some rural communities, these women are largely economically dependent on their male partners who decide their health, especially on sexual and reproductive healthcare issues or sometimes by an older woman who takes charge of the household (M. Kawonga & S. Fonn, 2008). This scenario further makes the challenges of screening more systemic. The healthcare system in South Africa lacks primary health-based care but is hospital-based, mainly focusing on curative care. While access to a primary healthcare facility for screening is possible, referral to the next level of care is delayed or not possible due to financial constraints. Another factor that hinders seeking health care by these women is the stigma associated with cervical cancer.

Of importance also is an agreement of two studies that were conducted in South Africa and Rwanda that the high prevalence of HIV infection is associated with cervical cancer; even a stronger association was observed in Rwandans (Mpunga et al., 2018; Stein, Urban, Weber, et al., 2008). Both high HIV infection experienced by women in South Africa and little or no access to cytology-based screening is a cause of concern. Other factors socially and economically identified as barriers to better health-seeking behavior exacerbate the situation. In South Africa, we need carefully planned comprehensive cancer control strategies to reverse this current situation. Supporting essential factors include a political commitment, good leadership, stewardship, and improved infrastructure for better health care delivery (Schneider, Barron, & Fonn, 2006).

2 LITERATURE REVIEW

I conducted the literature review from July 2018-March 2020 to collect background information on cancer, focusing on cervical cancer epidemiology, prevention, and early detection, including cytology screening in Africa, South Africa, and globally. Search engines used were Scopus, Google Scholar, Web of Science, PubMed, ScienceDirect, and Directory of Open Access Journal (DOAJ) using keywords like cancer epidemiology, cytology screening, HPV, HPV vaccination, HIV, and risk factors with a focus on cervical cancer. The English language was used for the entire literature search.

2.1 Cervix cancer epidemiology

Cervical cancer incidence in the 1940s in HICs such as Europe, North America, Australia, and New Zealand was similar to the current incidence in Africa. For example, it was 38.0 per 100 000 women in the USA at the Second US National cancer survey of 1947 (Dorn & Cutler, 1959). Even though the peak of this disease is at ages 40-50 years, it is possible to have a young woman diagnosed at the age of 30 years or even younger, unlike other cancers. Cervical cancer is also rated as one of the highest causes of disability and mortality at prime age. These women are expected to contribute to the economy and their families (Vaccarella, Laversanne, Ferlay, & Bray, 2017). Declining incidence rates were first observed at the beginning of the 21st century (Vaccarella et al., 2017). These declining rates were more observed after age 40, reflecting the effects of the national screening program mainly through cytology and lately HPV DNA testing (Bergstrom, Sparen, & Adami, 1999).

Conversely, cervical cancer in LMICs constitutes a significant public health problem with variations across regions (Vaccarella et al., 2017). As mentioned earlier, one of the factors increasing the risk of this cancer is the increased aging global population (Arbyn, Raifu, Autier, & Ferlay, 2007). In Africa, particularly in SSA, the incidence of cervical cancer seems to have increased over time, with the emergence of HIV/AIDS doubling the risk (Stelzle et al., 2021). However, no increases in the incidence of this cancer were noted, particularly in South Africa and Nigeria between 1960 and 1999 (Bergstrom et al., 1999). The highest incidence rates, up to 40 per 100 000 women, are found both in

Eastern and Southern regions of Africa. At the same time, the rest continent has lower rates with the lowest rates in the Northern area, according to the US Centers for Disease Control and Prevention (Bergstrom et al., 1999). Surprisingly, though HIV and AIDS have been endemic in Zimbabwe, no significant changes were observed in the cervical cancer incidence rates (Parkin et al., 2003). In Kampala, on the other hand, the increase in the incidence of this disease was observed before the AIDS epidemic onset (Parkin, 2008; Parkin, Whelan, Ferlay, Teppo, & Thomas, 2002; Wabinga, Parkin, Wabwire-Mangen, & Nambooze, 2000). Risky sexual behavior is amongst many risk factors associated with cervical cancer; however, HPV infection is the risk that accounts for 99% of disease causation. Scientific evidence showed HIV infection increases the risk (Stelzle et al., 2021). Unfortunately, women in SSA are hard hit because of the HIV infection epidemic. There is an urgent need to update information on cancer incidence in African countries where AIDS is endemic.

Bayo and colleagues, in their study, completed a detailed evaluation of the association between HPV and cervical cancer (Bayo et al., 2002). Bradford Hill criteria is a universally used guideline for evaluating the association between HPV and cervical cancer; however, IARC enhanced this guideline with special interpretation rules (IARC, 1995). Table 1. below presents critical criteria to be examined using a qualitative assessment to check the evidence.

Table 1. Causality criteria and their fulfillment by the association of HPV DNA and cervical cancer

		HPV and cervical cancer	
Criterion	**Concept**	**Type of evidence**	**Evidence**
Time sequence	Exposure must precede disease	Cohort studies to CIN 2/3	+++
Experimental (prevention)	Reduction of disease following reductions in exposure	Early vaccinations trials	+
Strength and consistency	High OR/RR Robust association in different settings	Case-control studies	+++
Biological plausibility and coherence	Mechanisms consistent with previous knowledge	Experimental	+++
Dose-response	The risk of disease is related to levels of exposure	Studies on the number of partners	+

Qualification of causality			
Necessary	Exposure is present in all cases	Detailed investigation on HPV-negative cervical cancer specimens. Explanation of alternative explanations	++
Sufficient	Exposure always leads to disease	Natural history of transient infections	

OR = Odds ratio, RR= relative risk, CIN= cervical intraepithelial neoplasia

Source: (Bosch, Lörincz, Muñoz, Meijer, & Shah, 2002)

2.2 Human papillomavirus (HPV) infection and cervical cancer pathogenesis

HPV combines more than 150 skin or mucus membranes of different kinds (Burd, 2003; IARC, 2007b; Rabkin, Biggar, Melbye, & Curtis, 1992; Schiffman, Castle, Jeronimo, Rodriguez, & Wacholder, 2007; zur Hausen, 2001). Sexually transmitted types of HPV are classified according to their carcinogenic potential either as 'high-risk' (HR) or 'low-risk genotypes (Fiander, 2011). The recent meta-analysis study by Guan and colleagues identified thirteen robust carcinogenic HPV genotypes (Guan et al., 2012) instead of initially fifteen (Fiander, 2011). These cause virtually all invasive cervical cancers (ICCs) worldwide, with HPV16, 18, and 45 the most problematic and highly carcinogenic genotypes (Bouvard et al., 2009). They are found more frequently in ICC than normal cytology samples. HPV 16 and HPV 18, the former causes squamous cell carcinoma, the most common, while the latter causes adenocarcinoma cancer which is less common but more aggressive (Burd, 2003; Rabkin et al., 1992; Walboomers et al., 1999; Woodman, Collins, & Young, 2007; zur Hausen, 2000). The other most frequent HR subtypes causing ICC by disease grade are HPV31, 33, 35, 52, and 58, with ICC:normal ratios ranging from 0.94 for HPV33 down to 0.44 for HPV52. It is essential to note that individual HR types differ enormously in their relative carcinogenic potential (Bouvard et al., 2009). In South Africa, the six most dominant HPV types were HPV-16 (34.7%), followed by HPV-35 (17.4%), HPV-58 (12.1%), HPV-45 (11.6%), HPV-18 (11.4%) and HPV-52 (9.7%) (Mbulawa, Phohlo, Garcia-Jardon, Williamson, & Businge, 2022).

HPV subtypes, 31 and 45, are primarily found in women in developing countries (Clifford et al., 2005). It is essential to note that other pre-invasive subtypes are less common. Of these less common, four HPV subtypes, 52, 53, 58, and 66, are found in women tested HIV positive who live in countries such as Asia, Thailand, South America, Brazil, and in Nigeria, Uganda, Zambia, and Cameroon countries of Africa (Akarolo-Anthony et al., 2013; Bruni et al., 2019; Sahasrabuddhe et al., 2007; Sukasem et al., 2011; Teixeira et al., 2018).

Scientific evidence confirms that HPV transmission is through sexual intercourse, the unprotected, and in the natural history of cancerous lesion development, HPV infection precedes. HPV is spread through direct skin contact and about 90% of HPV infections disappear unnoticed in a year or two without signs and symptoms, unlike other sexually transmitted infections. However, the remaining 10% of HPV infections, aided by the favorable environment to thrive on contact skin, may cause cervical intraepithelial neoplasia (CIN) (IARC, 2007b). These untreated dysplastic precursor lesions steadily and progressively develop into invasive cancerous tumors (IARC,

2007b). Hence, CIN precursor lesions are estimated to take 10 and 30 years to progress to a cancerous cervical tumor. Additional risk factors such as a weak immune system increase odds/risk for a cancerous tumor to develop. The increased odds/risk is also more common to women infected with HIV than to those who are HIV-negative (Clifford, Gonçalves, & Franceschi, 2006; Fiander, 2011; McDonald, Tergas, Kuhn, Denny, & Wright, 2014; Minkoff, Feldman, DeHovitz, Landesman, & Burk, 1998; Shiels et al., 2011). Based on these crucial findings that identified HPV infection as a precursor to a cancerous cervical tumor, it is not easy to accept cervical cancer with negative HPV. Rare cases with negative HPV were reported and believed to be an outcome of faulty detection methods or loss of HPV DNA during laboratory test processing (Tjalma, 2018).

A complex mechanism involving uncontrolled cell division triggered by an untreated or repeated HPV infection defines cervical cancer pathogenesis (Chan, Aimagambetova, Ukybassova, Kongrtay, & Azizan, 2019). The DNA can undergo cellular mutations and other favorable environmental conditions, leading to viral DNA integration (Chan et al., 2019). HPV infection histology includes a variety of cellular changes; hence its classification has specific terminology used. Three separate but interchangeable histopathological categories are currently used (Table 2).

Table 2. Grading schemes for pre-invasive histological abnormalities of uterine cervical squamous epithelium*

Dysplasia classification system	Cervical intraepithelial neoplasia (CIN)	Bethesda classification system
Mild dysplasia	CIN 1	LGSIL
Moderate dysplasia	CIN 2	HGSIL
Severe dysplasia	CIN 3	HGSIL
Carcinoma in situ	CIN 3	HGSIL

*Reproduced by permission from the Alliance for Cervical Cancer Prevention, 2003

The Bethesda classification encompasses the biological behavior of cervical squamous intraepithelial lesions (SILS) (Stoler & Schiffman, 2001) and classifies the abnormal squamous epithelial cells into four categories: (1) atypical squamous cells of undermined significance (ASCUS); (2) low grade squamous intraepithelial lesions (LSILS), light dysplasia/cervical intraepithelial neoplasia (CIN) 1 in addition to HPV associated cell changes; rates of regression of CIN 1 appear to be up to 60%, with progression rates of only 10% (Melnikow, Nuovo, Willan, Chan, & Howell, 1998; Ostör, 1993). It is not clear whether it is reasonable to treat these lesions or not. Two studies; (Flannelly et al., 1994; Shafi & Luesley, 1995) argued that it is safe to monitor women with cytological follow-up rather than the commonly employed practice of immediate excision. An HPV DNA test should supplement this after 12 months; if positive, refer for further investigation such as colposcopy. (3) high-grade squamous intraepithelial lesions (HSIL), with moderate dysplasia/CIN 2; do have a 40% chance of regression. Regression of both CIN 2 and 3 during pregnancy is minimal; however, there is spontaneous regression postpartum and carcinoma in situ/CIN 3, which have a 30% probability of progression to the invasive tumor; and (4) squamous cell carcinoma (Kurman & Solomon, 1994; Naucler et al., 2007; Nayar & Wilbur 2015; Stoler & Schiffman, 2001).

While the immune system typically clears the virus from the body within two years, HIV-infected women with immuno-suppression have a higher chance of persistent HPV infection that progresses to a cancerous lesion (Massad et al., 2001). Consequently, it is common for HIV-infected women to have increased rates of atypical squamous cellular cytological abnormalities even after treatment (Holcomb et al., 1999). Besides cervical cancerous lesions, some individuals with a persistent HPV infection can also

have other cancer types, such as the vulva and vaginal cancer (Bansal, Singh, & Rai, 2016).

2.3 Risk factors for cervical cancer

Cervix uteri carcinoma represents about 80% of the HPV attributable cancer burden, with women bearing around 90% of the HPV attributable cancers globally (de Martel, Georges, Bray, Ferlay, & Clifford, 2020; IARC, 2007b). Table 3, which was reproduced by permission from the source, shows HPV attributable cancers in developing and developed countries.

Table 3. Global burden of cancer attributable to infections in 2018: A worldwide incidence analysis

Site	**Human papillomavirus (HPV)**					
	Men New cases	**New cases attributable to infectious pathogens**	**Women New cases**	**New cases attributable to infectious pathogens**	**Total New cases**	**New cases attributable to infectious pathogens**
Cervix uteri carcinoma	-	-	570 000	570 000	570 000	570 00
Anus squamous cell carcinoma	9900	9900	19 000	19 000	29 000	29 000
Vagina carcinoma	-	-	18 000	14 000	18 000	14 000
Vulva carcinoma	-	-	44 000	11 000	44 000	11 000
Penis carcinoma	34 000	18 000	-	-	34 000	18 000
Oral cavity cancer	190 000	3900	91 000	2000	280 000	5 900

Site	Human papillomavirus (HPV)					
Oropharynx carcinoma	110 000	34 000	26 000	8 100	140 000	42 000
Larynx carcinoma	150 000	3 600	22 000	1 000	180 000	4 100
All sites	**-**	**69 400**	**111 500**	625 100	-	694 000
Source: (de Martel et al., 2020)						

HPV, as a specific cause of infection to the cancerous cervix, transmits efficiently through unsafe sex practices (Harper & Demars, 2014). The number of sexual partners to a female or their sexual partners increases HPV risk infection (Harper & Demars, 2014; Wen, Estcourt, Simpson, & Mindel, 1999; Winer et al., 2006). Many case-control studies showed a consistent association between the risk of HPV infection and early initiation of sexual activity at an early age of ≤ 18 years (Muñoz et al., 1992). Hence the use of condoms reduces the risk (Winer et al., 2006). Women marrying at young ages resulting in earlier age at first full-term pregnancy (< 18 years), have an increased risk of cervical cancer (Boyd & Doll, 1964). Married women are expected to be more knowledgeable of reproductive and sexual health topics through their visits to healthcare facilities. Thus, they have higher chances to access more accurate information from healthcare professionals (Elshami et al., 2021). In addition, married women may educate themselves by reading printed health materials distributed in clinics or using internet resources. On the other hand, single women in conservative communities, such as Palestine may feel inhibited to read or talk about sexual and reproductive health issues.

The ICC risk was 2.4-fold among those who reported early age (⩽16 years) of first sexual intercourse (AFSI) and age at first pregnancy compared (AFP) with those with both AFSI and AFP at ⩾21 years (Adoch et al., 2020; Louie et al., 2009). The importance of HPV-vaccination programs targeting young adolescents before first sexual intercourse can significantly decrease the incidence of cervical cancer. Additional efforts required include family planning, and sexual education adapted to the highly variable sociocultural contexts in the world. Counseling for delaying initiation of sexual intercourse, using condoms, and decreasing the number of sexual partners may prevent HPV infection and other sexually transmitted infections such as chlamydia, HIV, herpes simplex, etc. (Harper & Demars, 2014; Wen et al., 1999). Infection with HIV is strongly

associated with the incidence and persistence of HPV infection and advancement to invasive cervical cancer from squamous intraepithelial lesions (Harper & Demars, 2014).

Women of lower socio-economic status are at a higher risk for cervical cancer than the affluent (de Sanjosé, Bosch, Muñoz, & Shah, 1997). This high cervix cancer risk, rated as the highest globally, is noticed in women in SSA with some regional variation (De Vuyst et al., 2013). High HPV infection and cervical cancer are found in Eastern and Western Africa. An expected rise in cervical cancer incidence and mortality rates in SSA over the next 20 years is due to aging and growth and the concomitant HIV/AIDS) epidemic. High HPV risk accounts for the high incidence of cervix cancer, which is a consequence of the inability of SSA to either initiate or sustain cervical cancer prevention services. Furthermore, it is the most implicated cause of cancer death among women in the region in the same population (De Vuyst et al., 2013).

Other important factors that correlate with a social status include nutrition, genital hygiene, parity, smoking, other genital infections, and preventive services, especially screening. Also, HPV infection appears to be more prevalent in lower educational and income levels, including racial differences, black and white (Hildesheim et al., 2001). Studies that used cancer registries or death certificates observed excess relative risk for cervical cancer in women at job categories such as hotel and restaurant personnel, waitresses, cleaners, cooks, and woodworkers (Pukkala & Weiderpass, 1999).

Other risk factors include combining oral hormonal contraceptives for more extended periods. Tobacco use has increased the risk of squamous cell cervical carcinoma. The number of cigarettes smoked per day, including the length of time smoking, plays a significant role in increasing the risk (Harper & Demars, 2014).

2.4 Cytology-based screening, successes in developed countries

The WHO (2018) defines population screening as identifying disease before apparent signs and symptoms of that disease are experienced. A suitable and highly accurate test or examination is used, furthermore, easily applied with results accessible to the target population quickly. The test must be acceptable to the population, while the agreed policy is in place for identifying patients after testing, including referral and treatment procedures. Screening begins with an invitation to participate and ends with treatment for appropriately identified individuals at risk. A condition that affects the population of interest must be an important public health problem, with recognizable latent or early symptomatic stages.

Furthermore, epidemiologists must study the health problem well to understand its natural history. Tests must be cheap but effective to pick up the disease are critical points to consider while planning a screening program, ensuring that the program continues uninterruptedly (www. who/int/cancer/prevention/). The ultimate goal of the screening is to reduce morbidity and mortality due to cancer (Saslow et al., 2012).

Organized cytology-based screening programs adopted by wealthy countries achieved high coverage and reduced pre-cancerous lesions (Parkin, Bray, Ferlay, & Pisani, 2005; WHO, 2002). These countries have achieved screening coverage of 63% compared to only 19% in developing countries. Unfortunately, it has not been possible for developing countries to replicate this success story; hence cervical cancer burden increases with high morbidity and mortality rates (Bray et al., 2018; Sankaranarayanan, Budukh, & Rajkumar, 2001). SSA is one of the most affected regions and has access to only 5% of global resources for cervical cancer prevention (Denny, 2005; WHO, 2002).

Pap smear is a specific test for high-grade pre-cancerous lesions, but meta-analysis results reported an overall moderate sensitivity (Fahey, Irwig, & Macaskill, 1995; Nanda et al., 2000). It is estimated to have a mean sensitivity of 58% and specificity of 69% (Fahey et al., 1995). In the same Study by Fahey et al., they also noted variations in sensitivity for high-grade lesions even in individual studies, of which estimates had a mean of 47% (Nanda et al., 2000). Sometimes it is believed that both sampling and detection errors have contributed to the low-to-moderate sensitivity of cytology tests. High screening frequency is recommended to curb these cytology screening limitations to reduce the risk of cervical cancer in developing countries.

In addition, conventional cytology screening is liquid-based, and both do not show differences in sensitivity and specificity (Arbyn et al., 2008). However, cytology-based screening has been used for decades as the gold standard in the developed countries, including the United States, and reduced both morbidity and mortality due to cervical cancer by high proportions up to 60% (Fisher & Brundage, 2009; H. Hakama, Miller, & Day, 1986; M. Hakama, Chamberlain, Day, Miller, & Prorok, 1985; Miller, Chamberlain, Day, Hakama, & Prorok, 1990; Saslow et al., 2002). However, cervical cancer morbidity and mortality in specific sub-populations are still high. Most affected women, particularly in the United States, do not participate in the screening program due to deprivation circumstances such as less education, older, uninsured, or homeless; migrant workers face language barriers (Branković, Verdonk, & Klinge, 2013). Community-based awareness raising programs are some of the programs used to bridge the gap and successfully resulted in a decline in the prevalence of this disease (Peterson, Murff, Cui, Hargreaves, & Fowke, 2008). It is crucial that similar programs can be implemented on to the various groups of the population where women are at greater risk of having cervical cancer.

Other screening methods used in LMICs include the visual inspection with acetic acid (VIA), visual inspection with Lugol's iodine (VILI), and Human Papillomavirus (HPV) DNA testing. VIA, VILI, and HPV DNA testing should be combined with relatively simple, safe, and effective outpatient methods for treating pre-cancer lesions, such as cryotherapy or loop electrosurgical excision procedure (LEEP). However, each method has strengths and limitations that need to be considered in the national policy when choosing the proper screening method.

2.5 Challenges of cytology-based cervical screening in Africa

Many women in Africa die due to cervical cancer as they are unscreened or less participated in the screening (Bray et al., 2018). There are no organized screening programs in SSA, but pilot or research projects are usually discontinued after completion (Ntekim, 2012; Sankaranarayanan et al., 2001). South Africa is the only country in SSA with a national cytology-based screening program, but coverage remains poor, and the impact on invasive cervical cancer remains a challenge. The onset of the HIV/AIDS epidemic, which is the highest in the sub-region, has elevated the problem of cervical cancer to a severe level. The problem is limited resources in this region to address this problem (M. Kawonga & S. Fonn, 2008). While data from Uganda indicate that, at least in some areas of the country, substantial increases in the incidence of cervical cancer may have occurred (Wabinga et al., 2000), in Zimbabwe, there is no evidence of such an increase (Chokunonga et al., 2000). Cross-sectional/randomized screening intervention studies are ongoing in several African countries—Burkina Faso, Congo (Brazzaville), Ghana, Guinea (Conakry), Kenya, Mali, Niger, and Nigeria. Screening approaches such as cytology, HPV testing, VIA, and visual inspection with Lugol's iodine (VILI) were used (Goldhaber-Fiebert, Denny, De Souza, Kuhn, & Goldie, 2009; Johnson, Armstrong, Joyce, Teitelman, & Buttenheim, 2018; Ramogola-Masire et al., 2012; Sankaranarayanan et al., 2001; Snyman, Dreyer, Visser, Botha, & van der Merwe, 2015; Sossauer et al., 2014; Untiet et al., 2014). South Africa adopted a cytology-based national screening program for cervical cancer in 1999 as part of its National Cancer Control Policy (NDoH, 1999). After the situational assessment, every woman attending the public-sector services would be entitled to three free Pap smears per lifetime. The prescribed age is 30 years or older to start screening. A woman is expected to have ten years of space between each smear. The goal of this screening program was to screen in 10 years after implantation at least 70% of women in the country.

The screening program nationwide never had after the implementation evaluation raises concern. However, scattered studies evaluating the screening program were undertaken but confined to urban women. Program implementation was the main problem reported by these small-scale studies, which were conducted in Western Cape (Smith, Moodley, & Hoffman, 2008), the Free State (Cronje & Beyer, 2007), and KwaZulu-Natal (Sibiya & Grainger, 2007). These problems were associated with the level of recipients' knowledge about the screening, which translated to low target population coverage, health system implementation challenges, and fragmented health care services. Another vital factor observed was poor infrastructure, which indicates an unequal distribution of resources, common in South Africa. Resources, generally, are concentrated in urban areas while other parts of the country only offer essential healthcare services. Women from the rural villages only receive the proper care when traveling many kilometers to health facilities for investigations and confirmation of disease with advanced equipment. These are some of the crippling factors experienced in implementing intervention programs like the population-based cytology screening program. There is good benefit to women now and in the future if these challenges receive proper attention. Women's future generations will not succumb to cervical cancer, which is one of the well studied cancers and possible to prevent or detect it early for better survival.

Morbidity and mortality due to cervical cancer are high in the SSA, including South Africa. It is worrisome that South African women experience high cervical cancer incidence rates and low survival, especially where a free mass population-based cytology screening program is available as part of the National Cancer Control Policy. Screening is one of the cancer prevention and control strategies known to be effective. However, implementation is a great challenge and one of the neglected areas of cancer research in LMICs (Stewart & Wild, 2014). Is the mass population-based cytology screening program for cervical cancer available to the rural population of the Eastern Cape Province? This research aims to describe and track the incidence of cervical cancer investigate geographic differences, coverage of screening, and survival to inform the development of a successful intervention program in a rural setting, the Eastern Cape Province of South Africa.

3 AIM OF THE STUDY

The overall aim is to outline and describe the incidence of cervical cancer in a rural population in South Africa. Furthermore, investigate geographical differences, the extent of the coverage of screening programs, and the survival rate to inform the possible development of an appropriate intervention program. The specific objectives of the research, however, are:

1. To describe cervical cancer incidence in a rural population of South Africa for 1998-2012 using a population-based cancer registry. (Study I; articles 1 & 2).
2. To investigate the trends in the age-standardized and age-specific incidence rates of cervical cancer in two distinct geographic areas covered by the population-based cancer surveillance (Study II; article 3).
3. To describe cervical cancer trends and the screening program coverage based on routinely collected health service data by district health services (Study II; article 3).

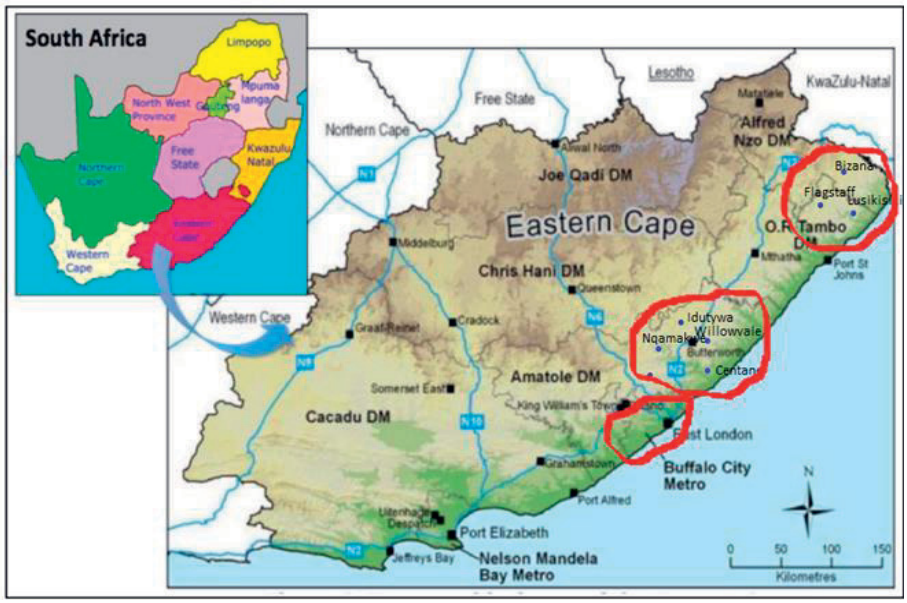
4 MATERIALS AND METHODS

4.1 Study design

4.1.1 Study population

The investigator conducted the entire research in a rural population in eight magisterial areas of the Eastern Cape Province in South Africa. These magisterial areas will be frequently referred to and constitute two distinct regions, northern and southern. The north region includes Bizana, Flagstaff, and Lusikisiki, while the south is Butterworth, Centane, Idutywa, Nqamakwe, and Willowvale (Figure 3). The population under study includes the one that focused on oesophageal cancer (OC) conducted by scientists at the South African Medical Research Council (SAMRC). They established a special cancer registry more than four decades ago. The registry focused on collecting oesophageal cancer cancers only on four selected magisterial areas, of which two had extremely high OC incidence rates areas; Butterworth and Centane and compared to the other two that had lower rates; Bizana and Lusikisiki (Jaskiewicz, Marasas, & Van der Walt, 1987; Makaula et al., 1996). In 1998 the special cancer registry was further developed and extended to be population-based (PBCR); the Eastern Cape Cancer Registry (ECCR).

Figure 3. Map showing cancer registration areas in the former Transkei region; Eastern Cape Province of South Africa



ECCR, as a population-based cancer registry, records all reported new cancer sites continuously and updates the database with new information. Only incident cancer cases of all ages who reside in the eight selected magisterial areas are recorded. ECCR covers just over 1.2 million population, 54% females and 46% males, based on the most recent population census in 2011 (StatsSA, 2012). It accounts for 16% of the population residing in the Eastern Cape Province with the age-sex composition in the population pyramid (Figures 4 (a, and b), typical of a rural setting.

4.1.2 Characteristics of the study population

The area covered by the cancer registry is mainly rural, with about only 30% population residing in a semi-urban area. More than 97% of this population are black Africans speaking isiXhosa, the local mother tongue. However, a high percentage of residents understand and speak English as well. This population supports both Christian and traditional norms and values. The main economic activity is subsistence farming, but much of the population relies on remittances from migrant labor in other parts of South Africa. Labor migration is historically significant in South Africa and may affect finding new cases and complete cancer registration coverage.

South Africa is an upper-middle-income country but experiences high unemployment, poor economic growth, and very high wealth inequalities. The study population includes communities with higher-than-average proportions living below the poverty line (StatsSA, 2018), the highest rate of HIV (NDoH, 2013a), and AIDS accounting for 31.5% of deaths experienced in the province (Msemburi et al., 2014).

The demography in these rural magisterial areas is typical of a developing country with about 43% of the population under 15 years of age (StatsSA, 2012). The age and sex distribution of the population, shown in Figures 4 (a) and (b), is typical of a rural population. Population structure shows a relative excess of children and older persons, particularly women, and a deficit of working-age adults, especially males. It reflects that the area is a labor reservoir. The number of children under five years of age is markedly smaller than the next age group (Figures 4 (a) and (b). Declining fertility can be one of the factors to explain this on the one hand and under-enumeration of young children on the other.

4.1.3 Cancer care facilities

The public healthcare delivery system in South Africa is based on a network of primary healthcare clinics, healthcare centers, district/secondary hospitals, and referral/tertiary hospitals provided by the government. Essential laboratory services are available in most public healthcare centers. Patients from the study population suspected to have cancer in the primary/local and secondary care facilities are mostly referred to Mthatha General Hospital Complex, which serves as a central referral/tertiary hospital for the region. The Nelson Mandela Pathology Laboratory, a regional state laboratory, is part of the National Health Laboratory Services (NHLS).

Patients with cancer are also referred for specialized services, including oncology and radiotherapy, to hospitals such as Inkosi Albert Luthuli (oncology services since 2003), King George V (with specialist thoracic surgery), King Edward VIII, and Addington hospitals in Durban, KwaZulu-Natal Province. These hospitals are accessible to patients from the northern region of the surveillance due to their geographical proximity.

Frere Hospital in East London with radiation and oncology unit is the only hospital in this region with oncology services and is one of the significant sources of the ECCR. It is a catchment area for both northern and the southern regions of cancer surveillance. Cecilia Makiwane Hospital is also a primary/local health facility accessible to southern region patients. The government provides transport to send cancer patients to these hospitals. However, patients must travel between 200 and 500 kilometers to get these specialized services and care. South Africa has a private health sector incorporating

medical practitioners, hospitals, and laboratory services that cater for about 20% of the South African population who have health insurance and can afford such care. The registry does not have access to private hospitals/healthcare facilities' data. However, there are no private hospitals in the area, and the proportion of this study population who uses private care would be tiny.

4.2 Study sampling and sample size

Sample for article 1 of study I was extracted from the ECCR database comprised of all new cancer incidents; topography C00-C80.9 (Fritz, Percy, Jack, Shanmugaratnam, & Sobin, 2000) for the period 1998–2002, whereas for article 2 were all new cancer incidents from the same database for 15 years; 1998–2012. For study II article 3, the investigator used two data sets: all women with cervical cancer; topography C53.0-C53.9 (Fritz et al., 2000) for 1998–2012. This 15-year period included an initiating period of the national cervical cancer-free cytology-based screening program in South Africa. The other data set had screening coverage data from the District Health Information System (DHIS), which is facility-based information collected monthly from all public-sector clinics and hospitals. A data element was collected from 2007 onwards, based on the number of women over the age of 30 who had a Pap smear is taken, an annualized indicator for screening coverage.

4.2.1 Data collection/case finding

Case finding was based on both active and passive methods for studies I and II. Hospital records were reviewed, and all patients with a residential address that belonged to the surveillance area were retrieved. The registry collaborates with all hospitals in the surveillance area and other significant public sector centers to the north and south. Public centres referred to are hospitals to which patients will be referred because of geographic proximity. Nineteen hospitals collaborate with the ECCR; eleven district/periphery/local, seven referrals, and one regional laboratory under the NHLS.

The active case finding method involved annual field trips undertaken by the ECCR staff who visit collaborating hospitals twice a year. Active case finding extended to all referral hospitals outside the registration area mentioned above. Part-time oncology nurses undertook passive case finding in certain hospitals who voluntarily collected data using a standardized cancer notification tool (appendix 1). They sent completed forms to the cancer registry monthly. Death certificates were not used as the source of

information as many deaths occurring in the registry area were not reported to the national death register. It is not compulsory in rural communities to report a death and get a certificate before burial. Verbal notification to the headman or chief before a funeral is always sufficient for any death in a village.

Study II additional data included screening coverage data that the investigator received from the DHIS. DHIS is facility-based information collected monthly from all public-sector clinics and hospitals. A data element was collected from 2007 onwards, based on the number of women over the age of 30 who had a Pap smear, an annualized indicator for screening coverage.

4.2.2 Data abstraction/collection tool

All studies used a specially designed standardized notification form as a data collection tool. The investigator developed the notification form based on international requirements (Appendix 1). Details on malignant cases were manually abstracted, excluding cases for which the primary site was uncertain. The investigator reviewed all records used for patient care, including out-patients and in-patients' registers and treatment records. Both active and passive data collectors used this form after receiving training from the investigator. Data collected for each patient included demographic variables tumor characteristics, including the site, type, and behavior.

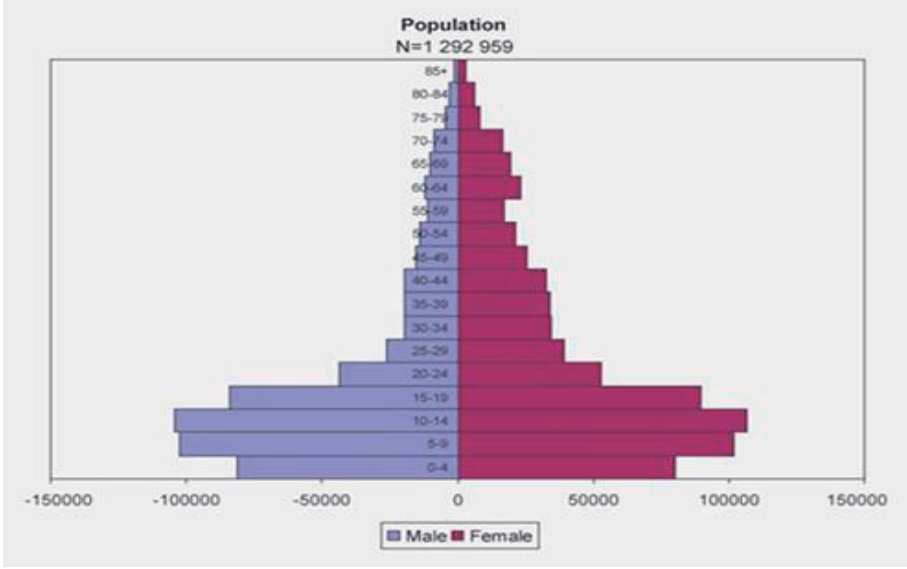
4.3 Data processing and storage

Cancer sites were manually coded in the registry for topography and morphology according to the third edition of the International Classification of Diseases for Oncology (ICD-O) (Fritz et al., 2000) for the descriptive studies I and II. Data were captured using the latest version of CanReg (Cooke, Parkin, & Ferlay, 2006; Ervik, 2012), which is a customized software computer program used by registries in Africa and other developing countries for cancer registration. CanReg was designed by the Unit of Descriptive Epidemiology of the International Agency for Research on Cancer (IARC). The investigator imported the second data set for study II to an excel spreadsheet. In preparation for analysis data were checked for accuracy and any discrepancies were verified and corrected by the investigator.

4.4 Population at risk

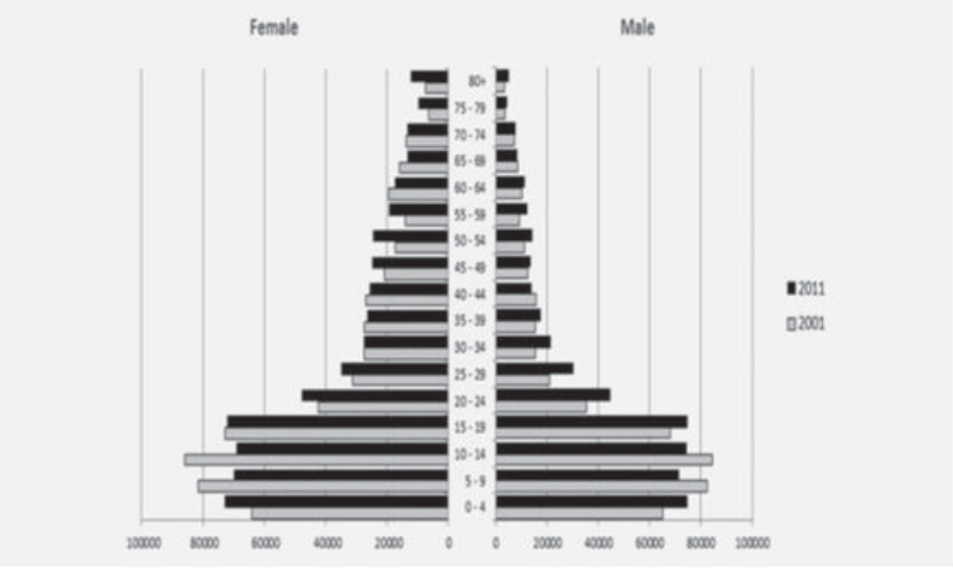
The 2001 census estimated the population at risk in 1998–2002 for study I, published as article 1. The distribution by age and sex at the censuses is shown in Figure 4 (a). Whereas for the same study but with results published in article 2, the population estimates used were 1996, 2001, and 2011 censuses providing age-sex specific counts of each of the eight magisterial areas (Statistics South Africa; Census counts by geography). For study II, article 3, the average annual population at risk was calculated for the three 5-year periods (1998–2002, 2003–2007, and 2008–2012). 1996, 2001, and 2011 censuses (StatsSA, 2011) provided age-specific counts of the population. The annual rates of change (by age, sex, and magisterial area) were used to prepare annual and 5-year period estimates. As described by Boyle and Parkin (1991), a direct method was adopted to calculate ASRs per 100,000 person-years. The world standard population was used as the reference population (Parkin, Whelan, Ferlay, Teppo, & Thomas, 1997). Weighted standard errors were calculated to provide 95% Confidence Intervals (CIs)for the ASRs.

Figure 4 (a). The estimated average annual population of eight magisterial areas for the period 1998-2002



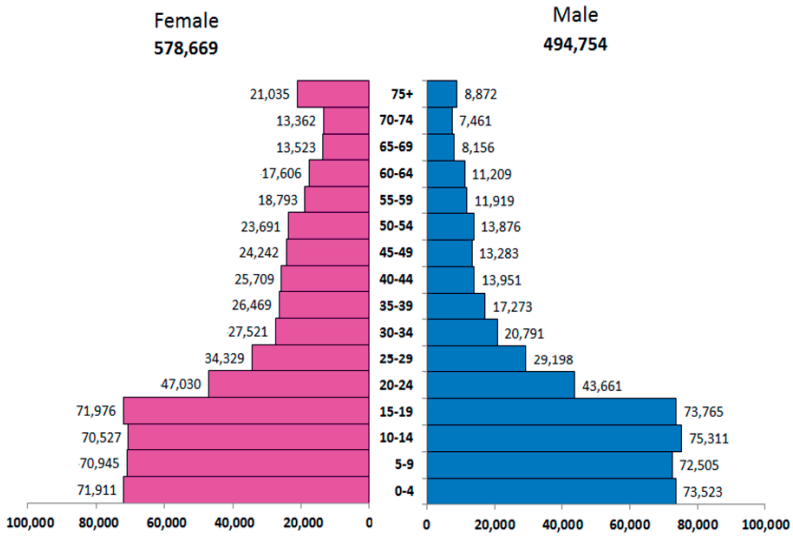
The annual rates of change (by age, sex, and area) in between these years were used to prepare annual estimates for 1998–2000, 2002–2010, and (based on annual change 2001–2011) (Figure 4a) for 2012 (Figure 4b).

Figure 4 (b). Population pyramids, 2001 and 2011 of eight magisterial areas, Eastern Cape Province, South Africa



Study II was published as article 3; the average annual population at risk for the whole population of the eight magisterial areas was calculated for the three 5-year periods (1998–2002, 2003–2007, and 2008–2012). (Figure 4c)

Figure 4 (c). The estimated average annual population of eight magisterial areas for the period of 2008-2012



4.5 Inclusion and exclusion criteria

Studies I and II included the only population with residential addresses in the registration area (Figure 3). Patients outside Eastern Cape Province and with other diagnoses were excluded.

4.6 Data analysis

Study I, which results were published as articles 1 and 2 covering two periods, 1998–2002 and 1998-2012. Data were cleaned, and a search was done for duplicate records based on name, age, sex, and diagnosis. Validity checks identified impossible codes and unlikely combinations. Only malignant cases were included in the analysis; patients outside the registration area were excluded. The number of incident cases is presented by age, sex, site, and method of diagnosis. Incidence and age-specific rates were estimated, including crude and age-standardized rates (ASR). Comparison of simple crude rates can give a false picture because of differences in the age structure of the populations to be compared (Boyle & Parkin, 1991). Since cancer is more common in older ages, crude rates are higher than younger ones. Thus, when comparing cancer

levels between two or more areas or investigating the pattern of cancer over time for the same area, it is crucial to allow for the changing or differing population age structure. The difference is accomplished by age standardization. A direct method was used in this analysis using the world standard population (Parkin et al., 1997) as a reference population.

Study I data were further analyzed for descriptive characteristics annual incidence rates calculated by 5 year age groups. Furthermore, the world standard population calculated age-standardized incident rates (ASRs). According to (Boyle & Parkin, 1991), a direct method was used. Population standard errors of the ASRs, and the ratio of the ASRs in pairs of periods (the standardized rate ratio (SRR), were calculated. The results of this analysis were published as article 2.

The 3rd article is the results of study II, which focused on cervical cancer only. The analysis of this study focused on the annual cervical cancer incidence trends calculated for the period 1998-2012. Results of this study are critical as they encompass the initiation period of the free national cytology screening program in South Africa. The age and stage distribution of incident cases (stages I and II versus III and IV) were checked, whereas the proportion of women diagnosed early in the progression of the disease was also assessed. Furthermore, the proportion of women with histology reports was checked. These reports confirmed cancer diagnoses. Sub-analyses were conducted for the region's distinct northern and southern areas covered by the registry. Screening coverage data analysis included the DHIS population.

4.7 Ethical consideration and permissions

Law governs access to health information in South Africa and, therefore, since cancer registration activities deal with patients, information falls within that law. The legal documents used as reference include the Promotion of Access to Information Act (NDoH, 2020) as amended, National Health Act (NDoH, 2003), Ethics in Health Research: Principles, Structures and Processes (NDoH, 2004), National Policy Framework and Strategy on Cancer in South Africa (NDoH, 2018) and National Health Act on the Compulsory Registration of Cancer (NDoH, 2011). The South African Medical Research Council Ethics Committee approved the main study proposal, cancer surveillance, on the 30th of August 2000 as amended by Protocol ID No. EC014-10/2014 on the 23rd of February 2014, and annually after that; 2015–2020. The Eastern Cape Health Research Committee approved the research permission No. EC RP52-33 on 12 May 2015.

5 RESULTS

5.1 Study I: Cancer incidence in a rural population of South Africa, 1998-2002

Information about disease burden is essential for monitoring the health of the nation. This cancer registry covers a population of about 1.8% of the total population of South Africa. As it aligns itself with findings of studies by (Parkin, 2008; Piñeros et al., 2017), it provides unbiased cancer incidence and is also valuable for monitoring cancer control programs and evaluating the effectiveness of those programs that include cytology-based screening for cervical. In South Africa, a middle-income country, such information is relatively sparse, including cancer incidence and mortality data. This article reports cancer incidence for the rural population of South Africa. This study will form baseline information for other studies and includes the extended surveillance area.

5.1.1 Descriptive characteristics

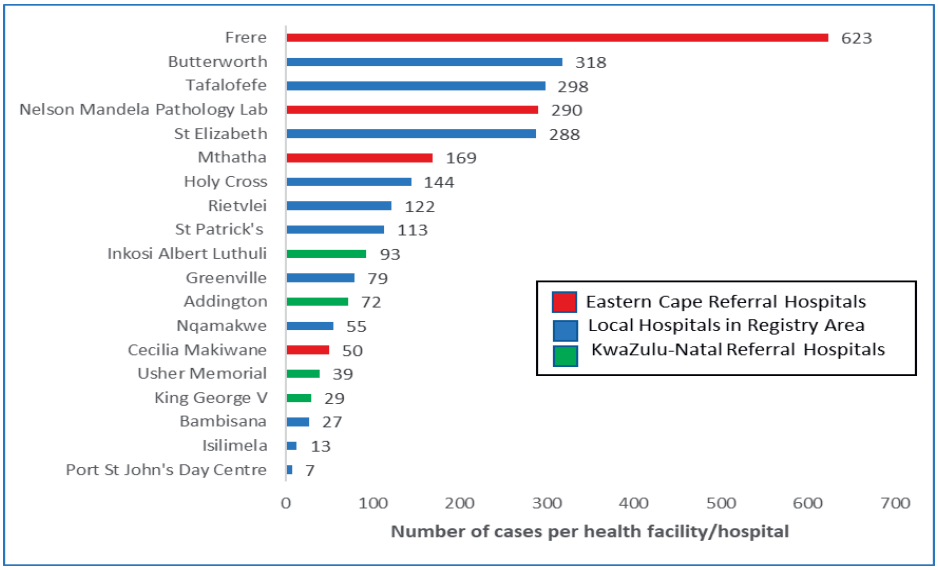
A total of 2,501 were new cancer cases reported for the period 1998–2002. There were 1,022 (40.9%) males and 1,479 (59.1%) females (Table 1). The number of cases was fairly consistent, with an annual average of 500 per annum (204 males and 295 females). However, incident numbers in 1999 and 2000 were lower than average (452 and 430, respectively). The average age at diagnosis was 56.2 years, with most cases in 50–74 years.

Table 4. Number of cases recorded each year by sex, 1998-2002

Year	Male	Female	Total
1998	234	389	623
1999	181	271	452
2000	196	234	430
2001	272	328	600
2002	261	358	619
1998-2002	1022	1479	2501

The number of cases contributed by each collaborating hospital is shown in Figure 5. Hospitals in the surveillance area contributed 57.2%, whereas referral hospitals 42.8%. The most significant number of cases came from Frere Hospital, a referral radiation-oncology hospital in the region. Referred patients from the surveillance area travel between 100 km; those from the southern area, which is closer, and 600 km from the northern area, farther away.

Figure 5. Total number of cancer cases by source, 1998-2002



A total of 1,130 cases (45.2%) were diagnosed based on clinical information only, without histological confirmation (Table 5). The clinically only basis of diagnosis includes radiology, scan, and biochemical/ biological tests such as alpha-feto test for liver cancer protein sensitive antigen (PSA) for prostate cancer. Shortage of specialists such as oncologists, including limited resources such as a laboratory, is an expected scenario in a rural setting where inequities exist. In addition, oesophageal cancer is prevalent in this population both males and females accounted for 75.8% of all cancers reported during this period, of which only 25.2% diagnoses had histology verification. Doctors can diagnose oesophageal cancer based on signs and symptoms only. History of progressive difficulty in swallowing starting with solids then soft diet and eventually liquids including one's saliva, progressive loss of weight, loss of appetite, vomiting, hoarseness to total loss of voice are signs and symptoms that are typical to oesophageal cancer. A barium swallow is another means of confirming the location of a tumor in the oesophagus. Occasionally patients also come very late when further investigations such

as a biopsy, including oesophagoscopy rather than being helpful, complicate the disease. A total of 1371 (54.8%) diagnoses had histology or hematology or cytology confirmation (Table 5).

Table 5. Most valid basis of diagnosis, 1998-2002

Method of diagnosis	No. of cases	Percentage
Clinical*	1130	45.2
Histology#	1371	54.8
Death certificate only (DCO)	-	-
Total	2501	100.0

* Clinical= clinically only, x-rays, scans, surgery

\# Histology= histology of primary site/metastasis, hematology, and cytology

5.1.2 Quality indicators

A total of 1,172 cases had a laboratory report, of which 981 also had a hospital report. A total of 2,301 patients had a hospital report, with hospitals in the registration area contributing 1,473 cases (64.0%) and the referral hospitals, including the state pathology laboratory, contributing 1,032 patients (44.9%), 204 patients were notified from both sources. With 1,431 cases notified from hospital records only, 191 from laboratory reports only, and 981 from both sources, the maximum likelihood estimates of the number of patients missed (not reported from either) is 259, indicating completeness of case ascertainment of 90.6% (95% CI 89.5–91.7%).

5.1.3 Cancer profile during 1998-2002 observation period: adults

Table 6 (a) and (b) shows the number of reported cancers by primary site, age group, and sex, together with the percentage frequency, crude, and age-standardized incidence rates. The age-standardized incidence rates for all cancers were 73.1 per 100,000 in males and 64.1 per 100,000 in females.

Table 6(a). Incident cases by age and sex and annual incidence rates (crude and age-standardized) by site, 1998–2002

Males	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	All ages	% Of total	HV%	Crude	ASR	ICD-10
Lip	0	0	0	2	0	0	0	0	2	0.2	100.0	0.1	0.2	C00
Tongue	0	0	0	2	5	10	8	4	29	2.8	86.2	1.2	2.1	C01-C02
Mouth	0	0	0	3	7	9	7	4	30	2.9	70.0	1.3	2.3	C03-C06
Salivary glands	0	1	0	0	1	0	0	0	2	0.2	100.0	0.1	0.1	C07-C08
Tonsil	0	0	0	0	1	2	3	1	7	0.7	100.0	0.3	0.5	C09
Nasopharynx	0	0	0	0	1	0	0	0	1	0.1	100.0	0.0	0.1	C11
Hypopharynx	0	0	0	0	1	0	1	0	2	0.2	100.0	0.1	0.2	C12-C13
Pharynx unspec.	0	0	0	0	0	4	0	0	4	0.4	100.0	0.2	0.3	C14
Oesophagus	0	0	2	24	80	128	166	44	444	43.4	16.2	18.9	32.7	C15
Stomach	0	0	3	2	6	3	5	2	21	2.1	38.1	0.9	1.6	C16

Males	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	All ages	% Of total	HV%	Crude	ASR	ICD-10
Small intestine	0	0	0	0	0	1	0	0	1	0.1	100.0	0.0	0.1	C17
Colon	0	2	2	3	3	2	4	1	17	1.7	70.6	0.7	1.2	C18
Rectum	0	0	1	1	1	1	4	1	9	0. 9	55.6	0.4	0.6	C19-C20
Anus	0	0	0	1	0	0	0	0	1	0.1	100.0	0.0	0.1	C21
Liver	3	3	4	7	19	5	13	8	62	6.1	6.5	2.6	4.4	C22
Gallbladder etc.	0	0	0	0	0	1	0	0	1	0.1	0.0	0.0	0.1	C23-C24
Pancreas	0	0	1	0	3	2	2	1	9	0.9	11.1	0.4	0.7	C25
Larynx	0	0	0	0	6	12	10	6	34	3.3	88.2	1.4	2.5	C32
Trachea bronchus lung	0	2	0	6	19	26	19	2	74	7.2	67.6	3.1	5.8	C33-C34
Bone	2	1	0	2	2	2	2	0	11	1.1	100.0	0.5	0.7	C40-C41
Melanoma of skin	0	1	0	2	2	3	2	0	10	1.0	80.0	0.4	0.8	C43
Other skin	0	0	0	0	1	3	5	0	9	0.9	77.8	0.4	0.6	C44

Males	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	All ages	% Of total	HV%	Crude	ASR	ICD-10
Mesothelioma	0	1	0	0	2	0	0	0	3	0.3	100.0	0.1	0.2	C45
Kaposi sarcoma	0	2	4	8	5	1	0	1	21	2.1	10.0	0.9	1.6	C46
Connective soft tissue	2	3	0	0	1	5	2	0	13	1.3	100.0	0.6	0.8	C47; C49
Breast	0	0	0	0	0	0	3	2	5	0.5	100.0	0.2	0.3	C50
Penis	0	0	1	1	1	1	0	2	6	0.6	100.0	0.3	0.4	C60
Prostate	0	0	0	0	2	16	28	23	69	6.8	28.0	2.9	4.4	C61
Testis	0	0	1	0	0	0	2	0	3	0.3	100.0	0.1	0.2	C62
Kidney	13	0	0	2	1	0	1	0	17	1.7	29.4	0.7	0.7	C64
Bladder	0	0	0	0	2	0	5	2	9	0.9	55.6	0.4	0.6	C67
Eye	3	0	0	1	1	1	0	0	6	0.6	50.0	0.3	0.3	C69
Brain, nervous system	5	1	0	1	1	0	1	0	9	0.9	100.0	0.4	0.4	C70-C72
Thyroid	0	0	0	1	0	1	3	0	5	0.5	40.0	0.2	0.3	C73
Hodgkin disease	0	1	0	0	2	2	0	0	5	0.5	100.0	0.2	0.4	C81-C82

Males	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	All ages	% Of total	HV%	Crude	ASR	ICD-10
Non-Hodgkin lymphoma	1	1	0	1	1	1	0	0	5	0.5	60.0	0.2	0.3	C85; C96
Multiple myeloma	0	0	0	1	3	8	4	0	16	1.6	50.0	0.7	1.3	C90
Lymphoid Leukaemia	3	0	0	0	0	0	0	0	3	0.3	100.0	0.1	0.1	C91
Myeloid leukaemia	0	0	0	1	0	0	1	0	2	0.2	100.0	0.1	0.1	C92-C94
Leukemia unspec.	4	0	0	0	0	0	0	0	4	0.4	100.0	0.2	0.1	C95
Other and unspecified	2	1	1	3	7	12	12	3	41	4.0	0.0	1.7	2.9	Other
All sites Total	38	20	20	75	187	262	313	107	1022	100.0	36.6	43.4	73.1	-
All site but C44	38	20	20	75	186	259	308	107	1013	99.1	37.0	43.0	72.4	-
HV–Histologically verified, ASR–Age-standardized rate														

Table 6(b). Incident cases by age and sex and annual incidence rates (crude and age-standardized) by site, 1998–2002

Females	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	All ages	%Of total	HV%	Crude	ASR	ICD-10
Lip	0	0	0	1	0	1	1	0	3	0.2	100.0	0.1	0.1	C00
Tongue	0	0	0	0	0	0	2	1	3	02	33.3	0.1	0.1	C01-C02
Mouth	0	1	1	1	0	0	7	2	12	0.8	91.7	0.4	0.4	C03-C06
Salivary glands	1	1	0	0	0	1	1	0	4	0.3	75.0	0.1	0.1	C07-C08
Tonsil	0	0	0	1	1	0	0	1	3	0.2	2.0	0.1	0.1	C09
Nasopharynx	0	0	0	1	0	1	0	0	2	0.1	100.0	0.1	0.1	C10
Hypopharynx	0	0	1	0	1	0	0	1	3	0.2	66.7	0.1	0.1	C11
Pharynx unspec.	0	0	0	1	0	0	1	0	2	0.1	100.0	0.1	0.1	C14
Oesophagus	0	1	4	24	72	170	165	43	479	32.4	9.0	16.6	20.2	C15
Stomach	0	0	0	3	1	6	1	1	12	0.8	0.7	0.4	0.5	C16
Small intestine	0	0	1	0	0	0	0	0	1	0.1	100.0	0	0.1	C17

Females	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	All ages	%Of total	HV%	Crude	ASR	ICD-10
Colon	0	0	1	0	2	4	2	0	9	0.6	55.6	0.3	0.4	C18
Rectum	0	0	1	1	1	3	1	0	7	0.5	14.3	0.2	0.3	C19-C20
Anus	0	0	0	1	0	2	1	0	4	0.3	100.0	0.1	0.2	C21
Liver	0	1	0	5	4	5	3	2	20	1.4	15.0	0.7	0.9	C22
Gallbladder etc.	0	0	0	0	1	0	2	0	3	0.2	33.3	0.1	0.1	C23-C24
Pancreas	0	0	0	1	4	6	2	0	13	0.9	7.7	0.5	0.6	C25
Larynx	0	1	0	0	1	0	0	1	3	0.2	100.0	0.1	0.1	C30-C31
Trachea bronchus lung	0	0	0	0	2	3	0	0	5	0.3	80.0	0.2	0.3	C32
Bone	0	0	0	2	5	6	5	0	18	1.2	61.1	0.6	0.8	C33-C34
Melanoma of skin	1	1	0	2	3	2	1	0	10	0.7	100.0	0.3	0.4	C40-C41
Other skin	0	0	0	1	3	6	4	1	15	1.0	88.1	0.5	0.7	C43
Mesothelioma	0	0	1	2	0	3	4	0	10	0.7	92.2	0.3	0.4	C44

Females	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	All ages	%Of total	HV%	Crude	ASR	ICD-10
Kaposi sarcoma	0	2	2	1	2	0	0	0	7	0.5	42.9	0.2	0.3	C46
Connective soft tissue	1	1	2	1	2	0	1	0	8	0.5	100.0	0.3	0.4	C47; C49
Breast	0	1	8	38	42	35	29	9	162	11.0	74.7	5.6	7.5	C50
Vagina	0	0	0	0	1	0	1	0	2	0.1	100.0	0.1	0.1	C51
Vulvar	0	0	0	0	1	1	0	0	2	0.1	100.0	0.1	0.1	C52
Cervix uteri	0	2	28	68	107	133	117	36	491	33.2	72.9	17.1	21.7	C53
Corpus uteri	0	0	0	2	7	4	8	0	21	1.4	76.2	0.7	0.9	C54
Uterus unspec	0	0	0	4	1	5	3	2	15	1.0	40.0	0.5	0.6	C55
Ovary	1	0	2	1	4	9	3	0	20	1.4	85.0	0.7	0.9	C56
Placenta	0	2	3	2	1	0	0	0	8	0.5	25.0	0.3	0.4	C58
Kidney	3	0	0	0	0	1	0	0	4	0.3	25.0	0.1	0.1	C64
Bladder	0	0	0	1	0	2	3	1	7	0.5	85.7	0.2	0.3	C67
Other urinary organs	0	0	0	1	0	0	0	0	1	0.1	100.0	0	0	C68
Eye	7	0	2	0	0	0	2	0	11	0.7	63.6	0.4	0.4	C69
Brain nervous system	10	2	1	1	0	1	1	0	16	1.1	100.0	0.6	0.5	C70-C72

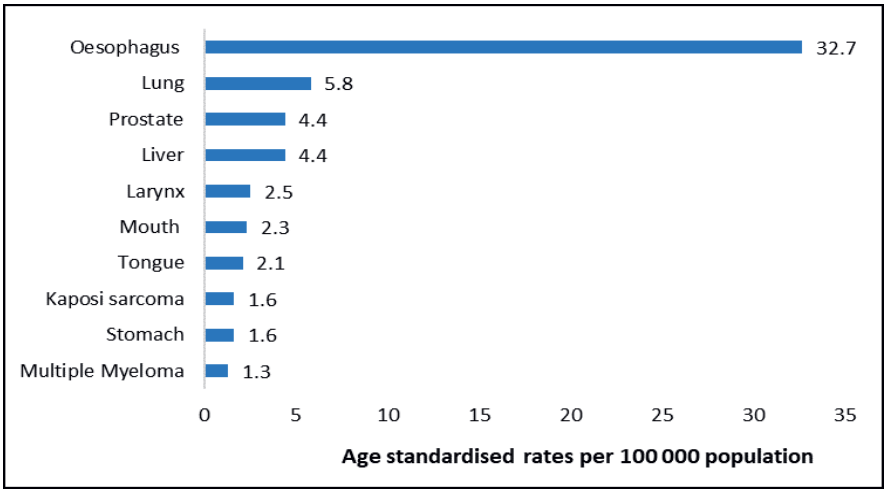
Females	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	All ages	%Of total	HV%	Crude	ASR	ICD-10
Thyroid	0	0	2	3	5	4	0	1	15	1.0	46.7	0.5	0.7	C73
Adrenal gland	1	0	0	0	0	0	0	0	1	0.1	100.0	0	0	C74
Hodgkin disease	2	0	0	0	0	0	0	0	2	0.1	100.0	0.1	0	C81
Non–Hodgkin lymphoma	0	2	1	2	2	0	0	0	7	0.5	85.1	0.2	0.3	C82-C85; C96
Multiple myeloma	0	0	0	0	1	3	1	1	6	0.4	50.0	0.2	0.3	C90
Lymphoid leukaemia	2	0	0	0	0	0	0	0	2	0.1	100.0	0.1	0	C91
Myeloid leukaemia	1	0	1	0	1	1	0	0	4	0.3	100.0	0.1	0.2	C92-C94
Leukemia unspec.	5	2	0	0	0	0	0	0	7	0.5	57.1	0.2	0.2	C95
Other and unspecified	0	0	1	2	2	7	5	2	19	1.3	0.0	0.7	0.8	Other

Females	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	All ages	%Of total	HV%	Crude	ASR	ICD-10
All sites Total	35	20	63	174	280	425	377	105	1479	100.0	48.9	51.4	64.1	-
All sites but C44	35	20	62	172	280	422	373	105	1469	99.3	49.2	51.0	63.7	-
HV–Histologically verified, ASR–Age-standardized rate														

5.1.4 Age-standardised incidence rates (ASRs) per 100 000 in males: 1998-2002

Figure 6 shows the ranking of the 10 cancers with the highest ASR, by sex. In males, the most frequently reported cancers were oesophageal (43.4%, ASR 32.7 per 100,000), lung (7.2%, ASR 5.8 per 100,000), prostate (6.8%, ASR 4.4 per 100,000) and liver (6.1%, ASR 4.4 per 100,000), larynx (3.3%, ASR 2.5 per 100 000), mouth (2,9%, ASR 2.3 per 100 000), tongue (2,8%, ASR 2.1 per 100 000), Kaposi sarcoma (2.1%, ASR 1.6 per 100 000), stomach (2.1%, ASR 1.6 per 100 000), multiple myeloma (1.6%, ASR 1.3 per 100 000).

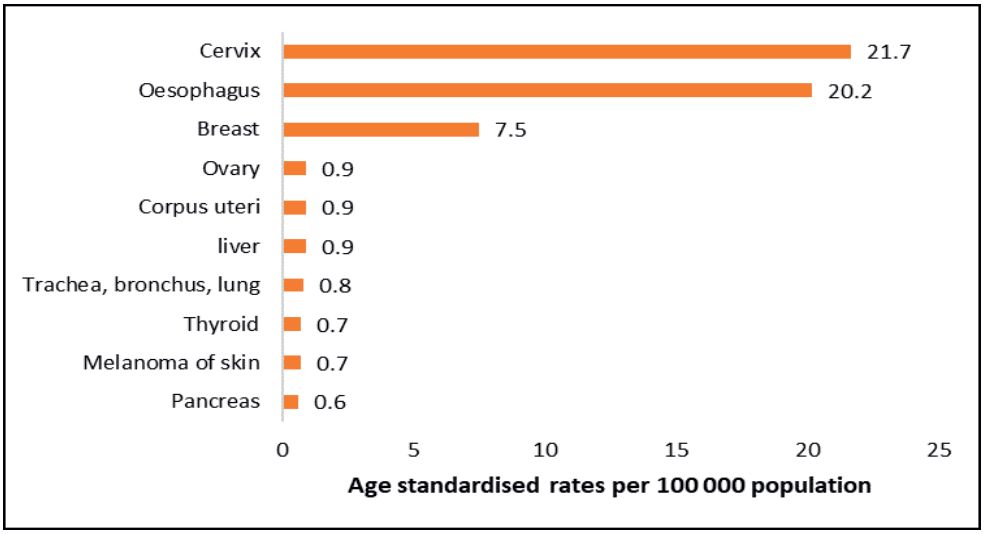
Figure 6. Age-standardized incidence rates (ASRs) per 100 000 in males, 1998-2002



5.1.5 Age-standardised incidence rates (ASRs) per 100 000 in females: 1998-2002

In females, the most common cancers were cervix (33.2%, ASR 21.7 per 100,0000), oesophageal (32.4%, ASR 20.2 per 100,000) and breast (11.0%, ASR 7.5 per 100,000), ovary 1.4%, ASR 0.9 per 100 000), Corpus uteri (1.4%, ASR 0.9 per 100 000), liver 1.4%, ASR 0.9 per 100 000, lung (1.2%, ASR 0.8 per 100 000), thyroid (1.0%, ASR 0.7 per 100 000, melanoma of skin (1.0%, ASR 0.7 per 100 000) pancreas 0.9%, 0.6 per 100 000.

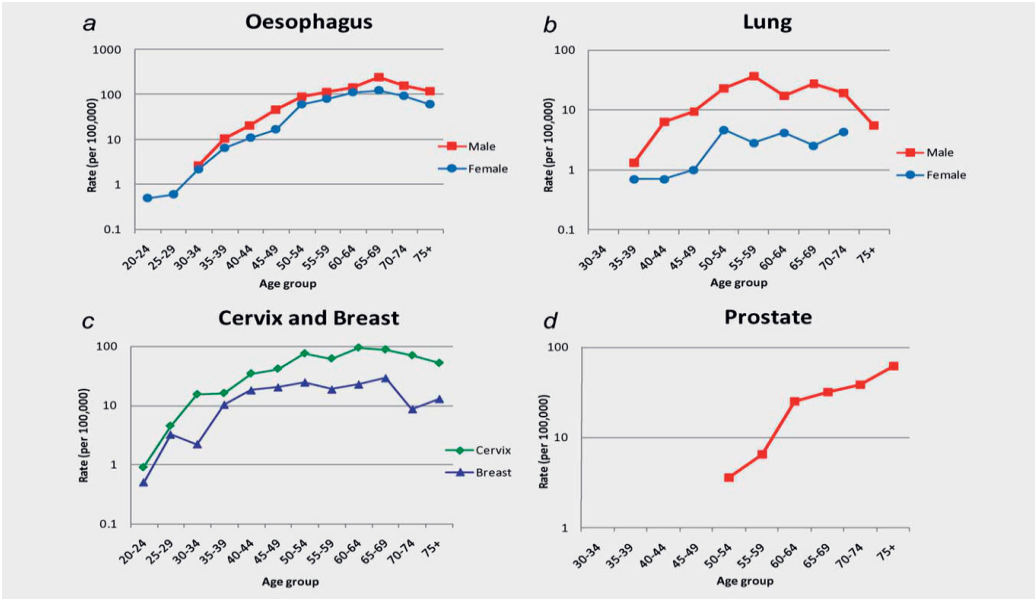
Figure 7. Age-standardized incidence rates (ASRs) per 100 000 in females, 1998-2002



5.1.6 Age-specific rates for the most common cancers: 1998-2002

Figure 8 shows the age-specific incidence rates for the most common cancers. The incidence of cancer of the esophagus increased steadily with age to reach a maximum at age 65–69, although the rates in females were lower at all ages. Lung cancer incidence rates in males increased markedly from age 35-39, reaching a peak at 55-59, whereas in females, the rates were 10-fold lower. Men aged 50 and over seem to be the most at risk for prostate cancer, and rates increase steadily with age. Cervical cancer incidence rates increased at ages 60–64; in contrast, breast cancer incidence rates were lower and became relatively constant after ages 40–44.

Figure 8. Age-specific incidence rates (log scales) for selected cancers, 1998–2002



5.1.7 Childhood cancers

There were 73 cases (boys and girls combined) of childhood cancers (0–14 years), which accounted for 2.8% of all cancers reported during the 1998–2002 period. In children, the most common cancers observed were nephroblastoma (15 cases), of which 80% were boys, brain tumors (15 patients); 60% were girls, leukemia (14 patients); 64.2% were boys, and retinoblastoma (11 patients); 72.7% were girls and neuroblastoma (10 patients); 60% were girls. Cancers with genetic predisposition (retinoblastoma and nephroblastoma) constituted 32.9%, half of which were from one magisterial area.

Table 7. Childhood cancers age 0-14; boys and girls

Cancer	Boys	Girls	Total cancers
Brain tumours	6	9	16
Nephroblastoma	12	3	15
Leukaemia	9	5	14
Retinoblastoma	3	8	11
Neuroblastoma	4	6	10
Other + unspecified	5	3	8
Total	39	34	73

5.2 Study I: Trends in cancer incidence in rural Eastern Cape Province; South Africa, 1998–2012

There are few cancer trends data reported in sub-Saharan Africa (SSA), notably due to the scarcity of PBCRs. The Eastern Cape Province PBCR is among the few SSA registries that report cancer data for a rural population. The researcher compared the incidence rates in this study in three five-year periods (1998–2002, 2003–2007, and 2008–2012).

5.2.1 Characteristics of registered cancer cases

In males, the most commonly diagnosed cancer during the 15 years was cancer of the esophagus; incidence rates showed a significant decline over the 15 years, entirely due to a 30% decrease between 2003–2007 and 2008–2012, to an ASR of 23.2 per 100,000 population. In contrast, prostate cancer had a more than doubled incidence of 9.9/100,000. It was the second most common cancer in men. In women, cancer of the cervix uteri has become the most common malignancy, with a significant increase in incidence during observation to 29.0/100,000. Oesophageal cancer is second in frequency, with (as in males) a considerable decline in the final ten years to an incidence of 14.5/100,000 in 2008–2012. The incidence of breast cancer increased by 61%, although the absolute rate remains low (12.2/100,000). The incidence rates of colorectal cancer were low, and the increases in incidence, although relatively large (35% in men,

63% in women), were not statistically significant. Although the incidence remains relatively low by southern African standards, Kaposi sarcoma dramatically increased incidence in both sexes (3.5-fold in men, 11-fold in women). Cancer prevention and control activities in the area need to be informed by these data and strengthened (Table 8).

The upper half showed the number of cases registered in the three periods, and the ASRs for the six cancers (and "all cancers") in males, and seven (plus "all cancers") in females. The ASRs in the three-time periods, with their 95% confidence intervals, are shown graphically in Figure 9. The standardized rate ratios comparing the ASRs in Period 2 (2003–2007) with those in Period 1 (1998–2002), Period 3 (2008–2012) vs. Period 2, and Period 3 vs. Period 1, with their 95% confidence intervals, are shown in the lower half of Table 8. The most commonly diagnosed cancers during the 15 years were cancer of the esophagus (1,280 patients in males, 1,424 patients in females); there was a significant decline in the ASR between Period 2 and Period 3 (but not earlier), so that, over the whole period, there was a significant 30% decrease in incidence in both sexes.

Table 8. Incident cases, annual age-standardized rates (ASR) per 100,000 population and standardized rate ratios (SRR) by site and sex for 1998–2002 (period 1), 2003–2007 (period 2), and 2008–2012 (period 3)

MALE

	Period 1 (1998-2002)			**Period 2 (2003-2007)**			**Period 3 (2008-2012)**		
	No.	**%**	**ASR per 10^5**	**No**	**%**	**ASR per 10^5**	**No**	**%**	**ASR per 10^5**
Oesophagus	444	43%	32.4	475	43%	32.8	361	30%	23.2
Large bowel	27	2.6%	1.9	34	3.1%	2.4	37	31%	2.6
Liver	62	6.1%	4.4	38	3.4%	2.8	65	5.4%	4.2
Lung	74	7.2%	5.8	68	6.1%	4.9	65	5.4%	4.2
Kaposi sarcoma	22	2.2%	1.7	42	3.8%	3.2	85	7.0%	5.8
Prostate	69	6.8%	4.1	106	9.5%	6.3	225	19%	9.9
All sites	**1 022**	**100%**	**72.5**	**1 114**	**100%**	**75.6**	**1 481**	**100%**	**76.6**

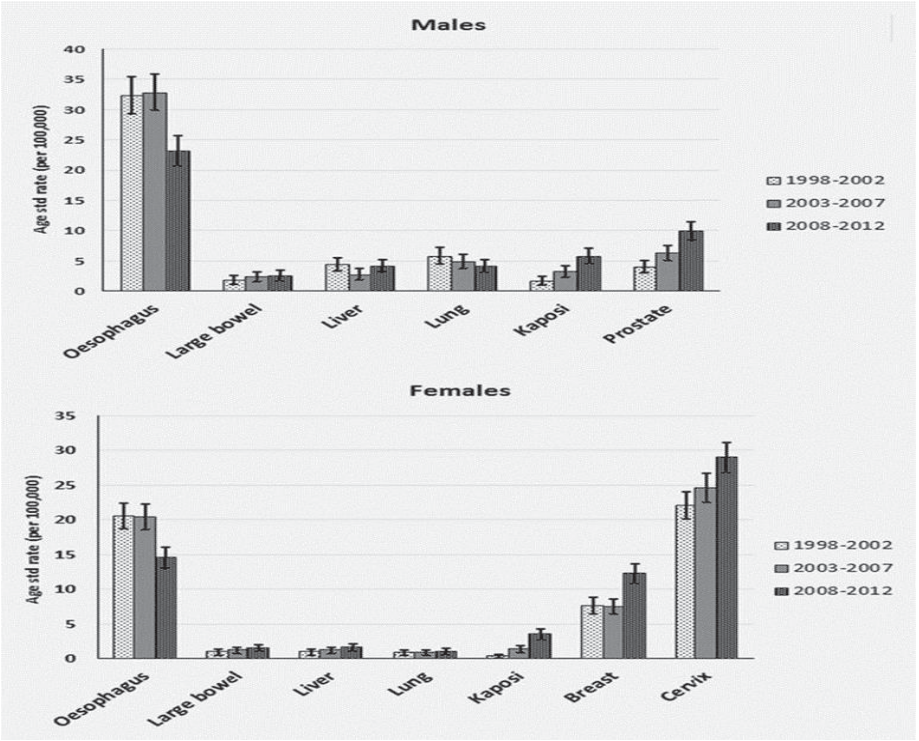
Period 2 vs Period 1				Period 3 vs Period 2			Period 3 vs Period 1		
	SRR	**95% CI**		**SRR**	**95% CI**		**SSR**	**95% CI**	
Oesophagus	1.01	(0.89-1.16)		0.7	(0.5-0.81)		0.72	(0.62-0.83)	
Large bowel	1.26	(0.75-2.11)		1.07	(0.67-1.72)		1.36	(0.81-2.24)	
Liver	0.63	(0.42-0.95)		1.49	(1.00-2.23)		0.94	(0.66-1.35)	
Lung	0.85	(0.60-1.18)		0.85	(0.61-1.21)		0.72	(0.51-1-02)	
Kaposi sarcoma	1.93	(1.15-3.23)		1.80	(1.25-2.59)		3.47	(2.24-5.36)	
Prostate	1.56	(1.14-2.12)		1.56	(1.23-1.99)		2.43	(1.85-3.20)	
All sites	**1.04**	**(0.95-1.14)**		**1.01**	**(0.93-1.10)**		**1.06**	**(0.97-1.15)**	
FEMALE									
Period 1 (1998-2002)				**Period 2 (2003-2007)**			**Period 3 (2008-2012)**		
	No.	**%**	**ASR per 10^5**	**No**	**%**	**ASR per 10^5**	**No**	**%**	**ASR per 10^5**
Oesophagus	481	32%	20.6	532	31%	20.4	411	20%	14.5
Large bowel	20	14%	0.9	29	17%	12	43	21%	1.5
Liver	21	14%	0.9	28	17%	12	42	20%	1.6
Lung	18	12%	0.8	30	12%	0.9	28	1.3%	1.0
Kaposi sarcoma	7	0.5%	0.3	31	18%	1.7	78	3.8%	3.5
Breast	162	11%	7.6	175	10%	7.5	299	14%	12.2
Cervix	491	33%	22.1	577	34%	24.6	719	35%	29.0
All sites	**1 481**	**100%**	**65.2**	**1 695**	**100%**	**69.6**	**2 080**	**100%**	**80.9**

	Period 2 vs Period 1			Period 3 vs Period 2			Period 3 vs Period 1		
	SRR	**95% CI**		**SRR**	**95% CI**		**SSR**	**95% CI**	
Oesophagus	0.99	(0.88-1.13)		0.71	(0.62-0.81)		0.71	(0.62-0.81)	
Large bowel	1.29	(0.73-2.29)		1.26	(0.78-2.04)		1.61	(0.96-2.76)	
Liver	1,27	(0.72-2.26)		1.31	(0.80-2.12)		0.66	(0.96-2.80)	
Lung	1.03	(0.54-1.98)		1.2	(0.66-2.15)		0.72	(0.68-2-26)	
Kaposi sarcoma	4.11	(1.94-8.69)		2.60	(1.74-3.90)		3.47	(5.83-19.65)	
Breast	0.99	(0.79-1.23)		1.63	(1.35-1.97)		2.43	(1.33-1.95)	
Cervix	1.12	(0.99-1.26)		1.18	(1.05-1.32)		1.31	1.17-1.48	
All sites	**1.06**	**(0.99-1.14)**		**1.17**	**(1.09-1.25)**		**1.24**	**(1.16-1.33)**	

Cancer of the cervix uteri continues to be the most common malignancy of women in the population under study (1,787 cases); there has been a marked increase in incidence with the ASR in the third five-year period, 31% higher than in the first (95% confidence interval of the SRR 1.17–1.48). The change in the incidence of breast cancer between Periods 1 and 3 was even more significant (SRR 1.61 (95% CI 1.33–1.95), entirely due to the considerable rise between the second two periods (2003–2007 and 2008–2012).

Cancer of the prostate more than doubled in incidence (SRR 2.43, 95% CI 1.85–3.20), but the most dramatic increases were for Kaposi sarcoma in both sexes (SRR in males 3.47 and females 10.70). Cancers of the colon/rectum showed quite significant increases over the 15 years in both sexes (SRR 1.35 and 1.63 in males and females, respectively), although non-significant because of the relatively small numbers of cases, while liver cancer increased in females (SRR 1.66 95% CI 0.99–2.80) but not in males. There were no significant changes in the incidence of cancer of the lung.

Figure 9. Age-standardized incidence rates (per 100,000 population) with 95% confidence intervals, for three time periods (1998–2002; 2003–2007; 2008–2012) in males (upper half) and females (lower half).



5.3 Study II: Article 3 Increasing cervical cancer incidence in the rural Eastern Cape Province of South Africa from 1998 to 2012: a population-based cancer registry study

This study investigated trends in the ASR and age-specific incidence rates in two distinct regions (the northern and southern areas) covered by the ECCR. In addition, the investigator used the routine health service data to assess the coverage proportion of cervical cancer screening program in the population under study.

5.3.1 Trends in the age-standardized and specific incidence rates

In this study, 1808 were new cervical cancers observed during the 1998–2012 period. The northern area of the cancer registry contributed 63%, whereas the southern just 37%. Table 1 shows the basis of diagnosis and the stage at diagnosis of these new

cervical cancer patients by area and period. Histologically verified diagnoses range between 65.8% and 71.3% in the northern area, 63.6%, and 77.7% in the southern area. Patients with only cytology reports and missing histo-pathology ranged between 5.8% and 13.6% in the northern area and 10.2% -10.4% in the southern area. The proportion of patients diagnosed clinically without further confirmatory tests ranges between 28.4% and 15.1% in the northern area and between 26.3% and 11.9% in the southern area. The percentage of women with histologically verified diagnoses was higher than those diagnosed clinically only. Histologically confirmed diagnoses ranged between 64.7% and 73.6%, while clinically diagnosed were between 27.4% and 14.0%. The smaller proportion of women with only cytology reports was between 7.9% and 12.5%.

Table 9. Basis of diagnosis and stage at diagnosis of cervical cancer occurrences by area and period, Eastern Cape Cancer Registry

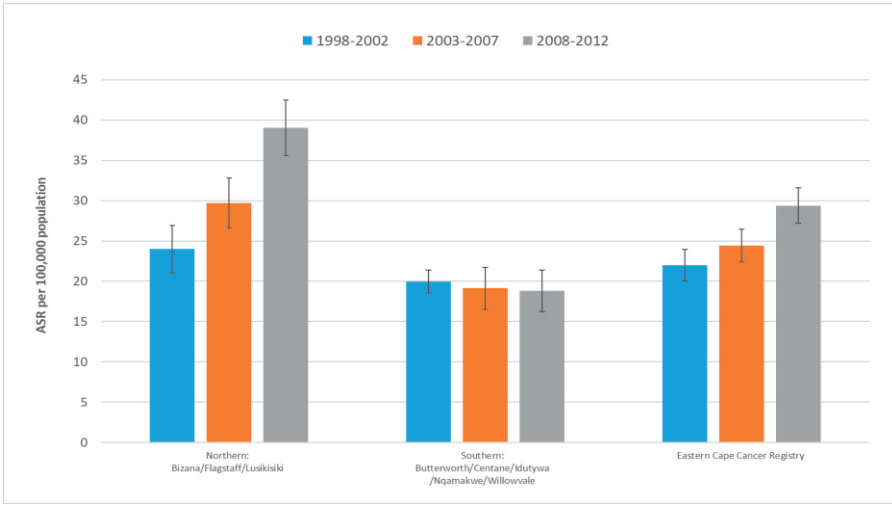
Northern Area		**1998-2002**	**2003-2007**	**2008-2012**
		N=265	**N=361**	**N=512**
Basis of diagnosis	% Histological	65.8%	59.6%	71.3
	% Cytological	5.8%	5.8%	13.6
	% clinical*	28.4%	34.5%	15.1
Stage at diagnosis	I		10.8%	8.9%
	II		19.5%	11.5%
	III		23.8%	24.7%
	IV		13.0%	8.7%
	Missing		33.0%	46.3%
Southern Area		**N=228**	**N=216**	**N=226**
Basis of diagnosis	% Histological	63.6%	66.1%	77,7%
	% Cytological	10.2%	9.2%	10.4%
	% clinical*	26.3%	24.8%	11.9%
Stage at diagnosis	I		18.0%	15.3%
	II		20.6%	15.8%
	III		23.6%	27.9%
	IV		14.6%	6.8%
	Missing		23.2%	34.2%

Eastern Cape Cancer Registry		N=493	N=577	N=738
Basis of diagnosis	% Histological	64.7%	62.0%	73.6%
	% Cytological	7.9%	7.1%	12.5%
	% clinical*	27.4%	30.8%	14.0%
Stage at diagnosis	I		13.4%	11.0%
	II		19.9%	12.9%
	III		23.7%	26.7%
	IV		13.6%	8.0%
	Missing		29.4%	42.4%

The ECCR collected stage of disease at diagnosis information from 2003 onwards. Consequently, Table 9 presents results for the two periods, 2003–2007 and 2008–2012. During 2003–2007, 29.4% of the occurrences had the missing stage at diagnosis, increasing to almost half (42.4%) in 2008–2012. The proportion with missing information about the stage was slightly higher in the northern area, ranging between 33.0% and 46.3%, and somewhat lower in the southern area, ranging between 23.2% and 34.2%. Stage III was the most common stage at diagnosis and increased from 23.7% in 2003–2007 to 25.7% in 2008–2012.

Cervical cancer ASRs per 100,000 of women are reported for three periods by area in Figure 10. Overall ASRs per 100,000 women were 22.0 (95% CI:20.0-24.0) in 1998-2002, 24.4 (95% CI:22.4-26.4) in 2003-2007 and 29.2 (95% CI:27.3-31.6) in 2008-2012. While the ASR in the entire region shows a progressive increase, the ASR in the southern area had a slight decrease over the period. ASRs per 100,000 women were 20.0 (95% CI:18.5-21.4) in 1998-2002, 19.1 (95% CI:16.5-21.7) in 2003-2007 and 18.8 (95% CI:16.2-23.4) in 2008-2012. These differences were not statically significant. In contrast, the ASR in the northern area increased significantly from 24.0 (95% CI: 21.1-27.0) in 1998-2002, to 29.7 (95% CI: 26.6%-32.8%) in 2003-2007 and 39.0 (95% CI: 35.6-42.5) in the period 2008-2012.

Figure 10. Age-standardized annual incidence rates for cervical cancer over a period by area, Eastern Cape Cancer Registry



The age-specific incidence rates are shown for the three periods in Figure 11A for the northern area and Figure 11B for the southern area. Incidence increased steadily by age, with a drop in the age group 70+ years. In the northern area (Figure 11A), a distinct increase was observed during the 3rd period 2008–2012 that occurred across all ages but was more marked in the 50–59 and 60–69 age groups. In the southern area (Figure 11B), the difference across the three periods was significantly low.

Figure 11(a). Age-specific annual incidence rates for cervical cancer over a period by area, Eastern Cape Cancer Registry

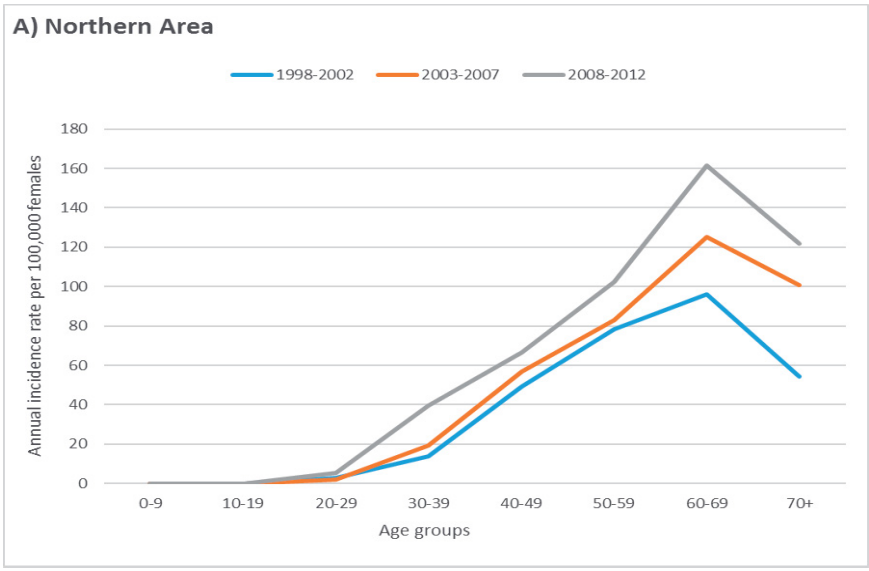
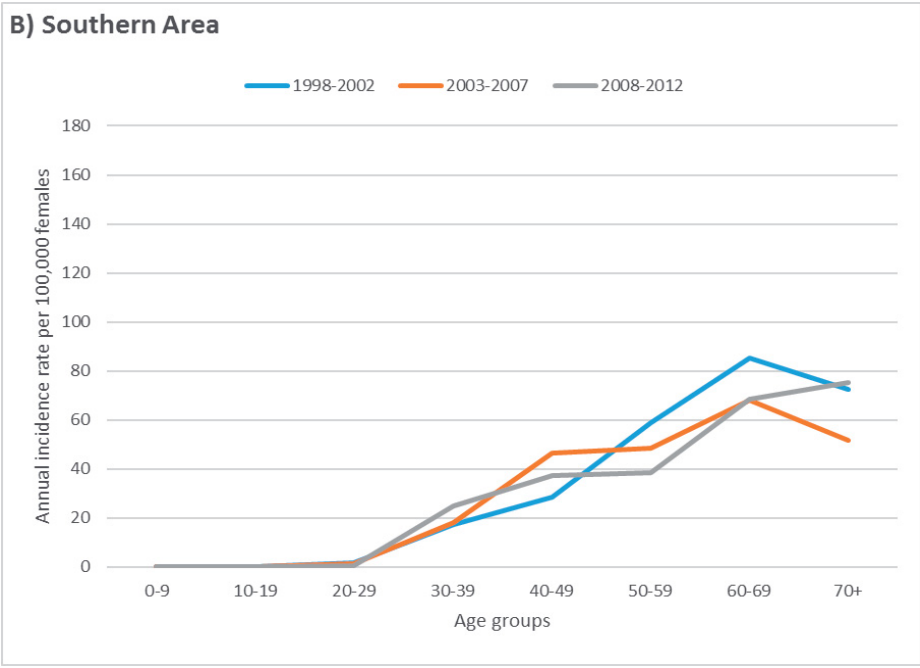


Figure 11(b). Age-specific annual incidence rates for cervical cancer over a period by area, Eastern Cape Cancer Registry



5.3.2 Screening coverage proportions

The cervical screening coverage results for women 30 years and older are shown by health sub-district and year in Table 10. A steady increase was observed from 2009 to 2012 to only 14.8% in 2012. The southern area, which spans two health sub-districts, reported slightly better coverage of the screening program, with an average of 7.7% in 2007. There was an increase to 41.0% in 2012, with anomalously high coverage of 69.0% reported for Mbhashe in 2010. Furthermore, this sub-district had almost twice the screening percentage of the Mnquma sub-district (52.3% vs. 29.7%) in 2012.

Table 10. Percentage of cervical screening coverage among women 30 years and older by area, 2007-2012

	Northern Area	Southern Area	
	Qaukeni Sub-District; Magisterial areas Bizana, Flagstaff, Lusikisiki	Mbhashe Sub-District Magisterial areas Idutywa, Willowvale	Mnquma Sub-District Butterworth, Centane, Nqamakwe
2007	2.2	7.9	7.5
2008	4.3	34.4	15.3
2009	10.6	43.8	16.4
2010	11.8	69.0	25.6
2011	14.8	46.6	30.0
2012	14.0	52.3	29.0

6 DISCUSSION

6.1 Main findings of the study

Study I dealt mainly with the description of cancer profile in the population residing in the rural region of the Eastern Cape Province. This study is critical because it was further used as a reference and guided the research undertaken. It also highlighted the usefulness of a population-based cancer registry that can track the high cervical cancer incidence experienced in this population that progressively increased over time. This study has temporal variations and spatial distribution of cervical cancer. Study II further explored cervical cancer incidence experienced, first-level evaluation of the cytology-based screening rolled out in this population. Are rates that we see compared to what was expected in the population with ongoing screening?

Initially, cancer registration in the Eastern Cape Province focused on oesophageal cancer (OC) until 1998, when the cancer registry expanded its scope and geographic coverage. Data collectors collected all cancer sites of all age groups and continuously updated them as long as the patient was still alive. The estimated completeness of case ascertainment was 90.6%. This was based on an independent check of findings by two people using the same resources of information which is referred to as capture-recapture. These two sources that were used included hospital notifications records and pathology reports. This estimate's main key factor is based on two sources independently using different detection sources (Parkin & Bray, 2009).

The overall ASR per 100,000 population for all cancers (excluding non-melanoma skin cancer) was 73.1 per 100,000 males, Table 6(a). Yet, in females, ASR was 64.1 per 100,000, Table 6(b). The top five cancers reported in males included the esophagus, lung, prostate, liver, and larynx, whereas in females were cervix, esophagus, breast, ovary, and corpus uteri. Oesophageal and cervical cancers largely dominated the ranking.

Table 11 compares selected most common cancers by magisterial areas. High OC incidence rates were observed in both males and females; in males with hotspots in magisterial areas that have been under observation for more than 60 years; Centane and Lusikisiki (48.3 per 100 000 and 43.2 per 100 000), respectively followed by Butterworth (32.1 per 100 000 and Nqamakwe (26.6 per 100 000). However, in females, regional variations in incidence rates were observed. The highest incidence rates observed were

in Centane (40.9 per 100 000) and Butterworth (23.2 per 100 000). The lowest incidence rates observed were in Idutywa (3.9 per 100 000).

Table 11. Age-standardized rates for most common cancers by magisterial area and sex, 1998-2002

Males Northern Area					
Magisterial area	**OC**	**Lung**	**Prostate**	**Liver**	**KS**
Bizana	37.2	9.6	2.1	4.9	3.3
Flagstaff	17.2	3.9	1.4	4.0	2.2
Lusikisiki	43.2	3.8	2.5	7.8	2.0
Males Southern Area					
Magisterial area	**OC**	**Lung**	**Prostate**	**Liver**	**KS**
Butterworth	32.1	8.7	14.6	1.9	1.1
Centane	48.3	4.5	5.4	5.3	0.0
Idutywa	18.5	4.5	3.2	1.0	1.6
Nqamakwe	26.6	8.0	5.6	4.6	1.0
Willowvale	19.9	3.4	3.4	1.7	0.0
Total	31.3	6.0	4.5	4.2	2.2

Females Northern Area					
Magisterial area	**Cervix**	**OC**	**Breast**	**Lung**	**KS**
Bizana	14.4	19.4	4.3	1.3	0.4
Flagstaff	26.4	17.2	4.8	0.0	0.9
Lusikisiki	29.6	19.9	10.0	0.2	0.5
Females Southern Area					
Magisterial area	**Cervix**	**OC**	**Breast**	**Lung**	**KS**
Butterworth	22.3	23.2	15.2	2.3	0.0
Centane	19.2	40.9	6.9	1.1	0.0
Idutywa	21.2	3.9	3.9	1.1	0.5
Nqamakwe	14.2	12.7	5.9	1.2	0.0
Willowvale	17.0	18.7	6.4	0.3	0.0
Total	20.2	18.0	7.1	0.9	0.8
KS = Kaposi sarcoma, OC = Oesophageal cancer					

Overall incidence rates reported for this rural population during the observation period appear low. Still, there are data from other populations in low-income countries to compare these rates. They are similar to the rates reported from the Gambia in 1997–1998 (Parkin, Bray, et al., 2005) and rates from the rural population of Barshi in India in 1988–1992 (Parkin, Whelan, Ferlay, & Storm, 2005). Table 12 compares the rates in the Eastern Cape (this study) with those recorded by the National Cancer Registry (NCR) (histologically diagnosed cases) (Mqoqi, Kellett, Sitas, & Jula, 2004) and by the cancer registry of Swaziland in 1996–1999 (Parkin et al., 2008). There is clear evidence of the distinct pattern in this area.

Table 12. Age-standardized incidence rates: Eastern Cape (1998–2002) (Mqoqi et al., 2004; NCRSA, 2012; Parkin et al., 2008); Swaziland cancer registry (1996–1999)

	Eastern Cape 1998-2002	**South Africa (Black;1999)**	**Swaziland (1996-1999)**
Cancer site			
Oesophagus	32.7	14.1	14.0
Stomach	1.6	3.6*	4.5
Colon & rectum	1.8	3.0	4.2
Liver	4.4	2.6	2.2
Larynx	2.5	4.1	4.5
Lung	5.8	9.3	10.1
Prostate	4.4	17.2	21.5
Kaposi sarcoma	1.6	2.8	17.2
Non-Hodgkin lymphoma	0.3	2.2	3.3
All sites	**73.1**	**97.1**	**145.3**
Female			
Oesophagus	20.2	7.0	4.1
Liver	0.9	1.3	5.2
Breast	7.5	18.4	12.1
Cervix	**21.7**	**34.9**	**59.3**
Uterus	0.6	4.7	5.6
Ovary	0.9	2.8	3.2
Kaposi sarcoma	0.3	1.5	9.5
Non-Hodgkin lymphoma	0.3	1.5	1.7
All sites	**64.1**	**103.7**	**134.8**
*1998			

Cervical cancer was the most common cancer observed with incidence rates of 18.8 (95% CI: 16.2–21.4) and 39.0 (95% CI: 35.6–42.5) per 100,000 women. Comparing these incidence rates with the global average, 6.8 per 100,000 women in 2012 (Ferlay et al., 2013) are very high. Furthermore, the incidence rates increased significantly over time, particularly in the northern area of the ECCR, contributing to the previously

reported overall increase (Somdyala et al., 2015). Several factors could be associated with the increasing trends, including increased population-based screening and the high prevalence of HIV. Conversely, the incidence rates in the southern area showed a slight decrease, which was not statistically significant.

The proportion of patients with only cytology reports increased in the northern area from 5.8% to 13.6% in the final period. In comparison, the percentage in the southern area remained stable at about 10% across the whole study period (2007 to 2012). The DHIS data showed that screening coverage increased in both study areas, albeit to less than optimal levels (Table 2). The southern area experienced better coverage during the study period, reaching levels of 41% in 2012, compared with the north, which had only 15%. Given the contrasting trends between screening and incidence, ascribing the high incidence rates in the north area to the increased access to the screening program appears unlikely.

Another factor known in this population is the prevalence of infection with HIV, including immunosuppression, mainly due to HIV infection. From historical data, breast cancer rates increase as cervical cancer rates decline. But data from cancer registries in South Africa, Uganda, and Zimbabwe showed an increase in both rates, which might be due to the prevalent HIV co-infection (Chokunonga, Borok, Chirenje, Nyakabau, & Parkin, 2013; Sitas et al., 2008; Somdyala et al., 2015). Even though cervical cancer is considered AIDS-defining cancer, conflicting trends are observed. Early reports found no association between HIV and the incidence of cervical cancer (Stein, Urban, O'Connell, et al., 2008). Pap test abnormalities at a younger age of 25 are associated with late-stage HIV infection (IARC, 2007). A study in South Africa by Moodley (2006) reported a reduction of invasive cervical cancer incidence between 1999 and 2003 in a high HIV prevalence area, concluding that cervical cancer cannot be considered an AIDS-defining condition in the African setting. The researcher further argued that women with HIV infection were dying before cancer could develop (IARC, 2007). Studies conducted in the post-HAART era have been equivocal. In 2009, the IARC Working Group on the Evaluation of Carcinogenic Risks to Humans found no apparent change in the incidence of cervical cancer among HIV-positive women (Gaym et al., 2007). However, studies based in Africa have seen a growing association between HIV and cervical cancer. Stein et al. (2008) observed an increased risk of cervical cancer associated with HIV (OR = 1.6, 95% CI: 1.3-2.0) in a case-control study conducted in Johannesburg, South Africa, while Mpunga et al. in their study (Mpunga et al., 2018) observed an even stronger association in Rwanda (OR = 5.9, 95% CI: 3.8-9.2) (Bouvard et al., 2009; Moodley, 2006). It is plausible that HIV-infected women are at increased risk of HPV, preinvasive cervical disease and, provided they do not succumb to AIDS and to invasive cervical cancer.

South Africa is in the throes of an HIV/AIDS pandemic that has affected both areas of the ECCR. In 2012, the prevalence of HIV among pregnant women was 30.0% in the OR Tambo Health District (incorporating the northern region) and 31.5% in Amathole Health District (comprising the southern region) (Massyn et al., 2014). Since 2008, there has been a country-wide roll-out of ART. Unfortunately, small area data on the provision of ART are unavailable. However, health service data point towards the possibility of a quicker roll-out in the northern area. Compared with a national average of 81.2%, the OR Tambo District reported that 86.2% of antenatal clinic pregnant women were confirmed HIV positive. These HIV-positive women started on ART compared with 61.9% in Amathole. The increased incidence of cervical cancer observed in the northern area is not associated with the screening program (Table 2). It may be the extent of HIV infection or associated with a quicker roll-out of ART in this area. We cannot say that a faster ART program roll-out equates with early initiation without specific information.

The Strategic Plan for the Prevention and Control of Non-Communicable Diseases identified the need to screen for cervical cancer in women with HIV and other sexually transmitted diseases at a younger age and more frequently (NDoH, 2013b). The high proportion of histologically verified diagnoses indicates good quality data. On the other side suggests the secondary level of care than the preventive. Presentation of patients at late stages of the disease may indicate that diagnosis was made by clinical signs and symptoms rather than screening. On the other hand, the high incidence rates may show the stability of cancer registration. However, combining the high incidence rates and advanced stages at diagnosis would mean a low screening reach with the population under study. Cytology-based screening does not perform well in SSA countries. During evaluation studies, only a few women were screened in South Africa and Botswana. Poor infrastructure and unplanned implementation are limiting factors to the excellent performance of cytology-based (Pap smear) testing (Cronje & Beyer, 2007; Mosavel, Simon, Oakar, & Meyer, 2009; Sibiya & Grainger, 2007), (Sibiya & Grainger, 2007; Smith et al., 2003).

In reviewing the cytology screening program implementation, Kawonga and Fonn (2008) identified the lack of attention to the health systems infrastructure (Denny, 2010). There is also a feeling that lack of consumer knowledge and empowerment leads to a low degree of health-seeking behavior (Botha & Richter, 2015). In addition, there is often a significant loss to follow-up after the initial screening test among women identified with abnormal cytology (Sibiya & Grainger, 2007). Other factors include unequal distribution of resources with less capacity available (Cronje & Beyer, 2007; Kaufmann & Schneider, 2008; Mosavel et al., 2009; Ramathuba, Ngambi, Khoza, & Ramakuela, 2016; Sibiya & Grainger, 2007). There is a great need to improve access to

infrastructure and human and material health services. Women with positive smears travel between 100 km and 600 km to access better care and management at tertiary hospitals in urban areas (personal communication with program managers).

The extent of screening programs coverage, the treatment outcomes, and the survival rate are essential to inform the possible development of an appropriate intervention program. In an unpublished study on treatment outcomes in this population, the default rate compares with other studies in Africa (Ezechi et al., 2014). Cancer patients relying on the state health system are increasingly struggling to access timeous treatment or delayed diagnosis and treatment until too late (Dobson, Russell, & Rubin, 2014). Other studies identified a combination of factors as the cause, such as distance from the treatment center & transport issues causing the delay or impossible to honor an appointment, misinformation about the disease, treatment side effects, and denial (Sharp et al., 2012).

The old traditional approach in medicine was to find and treat organic causes of disease and rarely incorporated psychological interventions into a patient's treatment plan as proactive measures (Jevne, Nekolaichuk, & Williamson, 1998). However, with the modern treatment trend, a comprehensive approach has been adopted in the care of patients that includes counseling (Jevne et al., 1998). There is also loss of income in some instances, and other losses experienced by cancer patients include role changes (Gegechkori, Haines, & Lin, 2017).

Other challenges included unpredictable disease courses with fear or the disease's reality. These challenges extend over a long period, and sometimes patients face the reality of depleted resources to survive (Gegechkori et al., 2017). The experience of living with a life-threatening illness fosters a unique shared partnership between the patient and the counselor ((Jevne et al., 1998). The desired outcome of this partnership is to re-establish and keep the patient's sense of self, despite an unpredictable and chaotic illness course (ibid).

6.1.1 Cancer surveillance

Dated back to the beginning of the 20th century, the generation of reliable and comparable cancer data through cancer registration became important and identified as an indispensable component of etiology research ((Jensen, Parkin, MacLennan, Muir, & Skeet, 1991). ECCR as a member of the International Association of Cancer Registries (IACR) since 1998, follows cancer surveillance processes and guidelines accordingly by experts in this field such as the WHO-IARC. Public health defines surveillance as a core

function of public health practice "the ongoing, systematic collection, analysis, and interpretation of health data essential to the planning, implementation, and evaluation of public health practice. That includes timely dissemination of this information to those who need to know and act upon that information" (Jensen et al., 1991).

ECCR collaborates with all sources accessible that generate cancer data in the surveillance area. They include enabling laboratory diagnostics to detect or confirm health conditions and information technologies to support the surveillance processes. Systems of surveillance are data collection, analysis, and dissemination. This activity's other essential components are a clinician for consultation and reporting purposes; a clinician, public health, and laboratory technician. Legislation, regulations, and policies guide those working in cancer surveillance. Good support through worker training and education ensures the sustainability of management. The principal objective of cancer registries is to describe and monitor time trends in the incidence of cancer (Parkin, 2006). In the last 20 years, the role of registries has expanded further to embrace the planning and evaluation of cancer control activities and the care of individual cancer patients (Parkin, 2006).

Cancer incidence statistics so far are widely available. In these studies, cervical cancer remains a public health problem. Unfortunately, it affects women at a critical time, negatively impacting their families' social and economic stability (Anorlu, 2008). The most recent study will use a global survey on cervical cancer incidence (Arbyn et al., 2020). This study provides updated estimates of the cervical cancer burden ten years after the 2008 GLOBOCAN publication. Findings identified cervical cancer as still a significant public health problem, ranking it as the fourth most common cause of cancer incidence and mortality in women worldwide. It is the leading cause of cancer-related deaths in eastern, middle, southern, and western Africa. The estimated age-standardized incidence of cervical cancer was 13·1 per 100 000 women globally and varied widely among countries, with rates ranging from less than 2 to 75 per 100000 women. The highest incidence affects approximately 79% of women in SSA at an age younger than 45 years. About 60–75% of women in SSA who develop cervical cancer live in rural areas (Parkin et al., 2008). While data from Uganda indicate that, at least in some areas of the country, substantial increases in the incidence of cervical cancer may have occurred (Wabinga et al., 2000). However, Zimbabwe showed the opposite observation (Chokunonga et al., 2000).

6.1.2 The Expanding Use of Surveillance Systems

The value of the registry is the usefulness of its data. The availability of a high-quality population-based cancer registration system is a critical component of any evidence-based cancer control program. While the global study (Arbyn et al., 2020) will act as baseline data on global initiatives set up to scale up preventive, screening, and treatment interventions to eliminate cervical cancer. The study in the rural population of the Eastern Cape in South Africa estimates the effect of the national screening program in this community since its roll out more than 20 years ago. With the urgent need for screening program review, the same study will act as a baseline after WHO calls for the cervical cancer control program scale-up.

The lack of effective screening and treatment strategies is significant for developing countries' sharply higher cervical cancer rates. Without access to viable programs, women from poor communities generally seek care only when they develop symptoms, and cancer at that stage is advanced and challenging to treat. About 70% of women diagnosed were already at advanced stages III and IV, indicating limited screening access. Poor survival of this disease is inevitable. It is confirmed by low relative survival results below 50% in both 3 and 5 years in studies conducted in this population (Allemani et al., 2018; Allemani et al., 2015; Sengayi-Muchengeti et al., 2020). And in the SSA region, a study by Bray et al. (2018) reported many women with cervical cancer who were unscreened or under-screened had the highest mortality rates. The findings above compare to small-scale studies in South Africa in different provinces, Western Cape (Smith et al., 2008), the Free State (Cronje & Beyer, 2007), and KwaZulu-Natal (Sibiya & Grainger, 2007). These studies' findings include unawareness of recipients about the program and service meant for them, which is questionable. Eventually, this translated to fewer women screened hence a high percentage presenting with the disease at late stages; III and IV. To compound the problem is the widespread lack of resources resulting in impossible preventative health initiatives for women (M. Kawonga & S. Fonn, 2008).

Historically, evaluation received greater attention, but monitoring is of increasing interest given automation and data-intensive systems growth. Results of a study in England, Scotland, and Wales showed a combination of reduced coverage and reduced quality of screening which led to a reduction in the diagnosis and treatment of CIN3 and, consequently, an increase in cancer. The increasing cervical cancer rates were also attributed to the rise in the underlying rate of human papillomavirus (HPV) infection, resulting in an increase in the underlying rate of disease in young women (Sasieni & Castanon, 2012).

The screening policy objective is to screen women from age 30 at ten years intervals. That compares with other studies, such as a study done by Sasieni, Castanon, Parkin. These data alone are not enough to determine the effectiveness of cervical screening in young women. Nevertheless, it should be clear that it is unreasonable to assume that, within ten years, a third or even 10% of the CIN3 treated in the United Kingdom in a woman aged 20–24 would otherwise have progressed to invasive cancer. In our view, those who wish to screen women under age 25 need to provide evidence that its benefits outweigh its costs both to society and to individual women.

Screening efforts have relied mainly on the Pap smear, an extended test to detect abnormal cell changes. However, while the test has achieved tremendous success in industrialized countries that offer periodic, high-quality screening, Pap smear programs are complex and costly to run and need concerted efforts to follow those with positive smears and due for repeat smears. The program has failed to reach a significant proportion of women in countries where health systems and infrastructure are poor. Other essential factors include accessibility of treatment through providing resources to treat, including cancer specialists. Of note, there is a meager doctor/population ratio in South Africa, especially in the rural hospitals with a high load of competing healthcare needs.

6.2 Strengths of this study

This study highlighted the need for ongoing population-based cancer surveillance in this region that identified a distinct cancer profile dominated by cervical cancer in women. Another important aspect highlighted was a demonstration of the usefulness of the registry in monitoring the burden of the disease and evaluation of the intervention, the cytology-based screening program. It also provided the government with the local data needed to prioritize and evaluate cancer control efforts to reduce the burden and suffering from cancer in the rural Eastern Cape Province community. Lastly, the cancer registry generated valuable information as the baseline for other three studies, including regional and global collaborative studies on cancer survival.

Data quality indicators showed completeness of case ascertainment of 90.6% (95% CI 89.5–91.7%) (Somdyala, Bradshaw, Gelderblom, & Parkin, 2010). Over time, the registry investigated trends in the ASR and age-specific cervical cancer incidence rates. Consistent monitoring of the disease burden identified an increase of persistent cervical cancer in this population, showing the opposite of predicted declining rates derived by modeling South African data (Forouzanfar et al., 2011).

Survival rates are a vital measure of the effectiveness of healthcare systems in the management of cancer patients, the goal of which is to provide policymakers with high-quality evidence with which they can act (Coleman et al., 2011). Women's relative survival of this cancer in the Eastern Cape is also low compared to other middle-income countries in Africa (Allemani et al., 2018; Allemani et al., 2015; Sengayi-Muchengeti et al., 2020). There is evidence that even minor improvements in survival from common cancers can prevent many premature deaths (Coleman et al., 2011). Information about disease burden is essential for monitoring the health of the nation.

In South Africa, a middle-income country, surveillance includes cancer incidence, survival, and mortality data, which is relatively sparse. A national pathology-based cancer registry, established in 1986, has provided limited information on the cancer burden based on voluntary reporting by pathology laboratories of invasive cancers diagnosed by histology, cytology, or hematology. Consistent cancer incidence information provided by the Eastern Cape Cancer Registry is a unique contribution to understanding cervical cancer's burden in South Africa. This registry is population-based, the only one in South Africa that counts in 1% of the SSA population, contributing to global cancer incidence.

6.3 Limitations

The Eastern Cape Cancer Registry has no access to private hospitals/healthcare facilities' data. However, there are no private hospitals in the surveillance area, and the proportion of this study population is less than 5% that uses private health care centers. 90.6% was a reasonably high level of ascertainment achieved from the data sources. However, under-diagnosis of cases may be an issue in this rural population, with difficulties accessing medical services.

Results showed a high percentage of cases with missing information about staging, ranging between 29.4% and 42.4%. That contrasts with the high rate of patients with histologically verified diagnoses. Until recently, the staging disease information at diagnosis is not part of mandatory variables collected by cancer registries. This information was only collected when available on patients' records during data abstraction. Furthermore, data collectors do not always have access to disease staging information. These results need careful interpretation. There is also a high likelihood of under-estimation of cytology as the basis of diagnosis in this study. Information on cytology reports is not always available from the patients' medical records kept in the

wards to which data collectors have access. Screening coverage proportions from the routine health data also need careful interpretation as they are based on aggregate data and may include repeat screenings of an individual woman. Hence, the coverage proportions may be even lower than reported.

Labor migration is historically significant in South Africa and might cause a lower cancer incidence than expected in the population under study. On the other hand, some patients diagnosed elsewhere might return home to die and inflate the incidence rate if they were not counted. However, this is likely to have a minor effect as only those patients who receive treatment at the collaborating health facilities are included in the register.

7 CONCLUSION AND RECOMMENDATIONS

There are fewer PBCRs in SSA; hence cancer incidence data are scarce (Parkin, 2008). Many competing health demands in SSA cripple the establishment and maintenance of PBCRs. However, cancer registration is still feasible in Africa despite the continent's challenges compared to developed countries. The Eastern Cape PBCR is among the few SSA registries that survived those challenges and generated credible data on cancer incidence in a rural population.

The study highlights the importance of cancer registration that tracked the high cervical cancer incidence experienced by women in the rural Eastern Cape Province that progressively increased over time with rates of 18.8 and 39.0 per 100,000 women (Somdyala et al., 2020; Somdyala et al., 2015). Both young and older women are affected by this disease starting at ages 30-39, with the highest peak at 40-49. The risk of this cancer continued up to 70 years and above. It became clear that factors may be contributing to these high levels of cervical cancer incidence in this area. These include the persistent infection of the cervix by the oncogenic types of Human Papilloma Virus (HPV 16 & 18), the most common factor and necessary cause in some 72% of cervical cancers in Africa (Denny, 2010; Sitas et al., 2008). Further, the incidence of HIV infections that affects 60% of women in South Africa is another contributing factor (Chibwesha et al., 2018; Chokunonga et al., 2013; Murray et al., 2014; UNAIDS, 2015; Wabinga et al., 2014). Systematic reviews studies and meta-analyses had shown that the overall risk of HIV infection in women doubled when they had a prevalent HPV infection with any genotype (Houlihan et al., 2012; Lissouba, Van de Perre, & Auvert, 2013; Taku et al., 2020).

In SSA, there are no organized screening programs for the early detection of precancerous lesions (Ntekim, 2012; Sankaranarayanan et al., 2001). Most screening activities exist for shorter research purposes or are a once-off intervention. South Africa adopted a cytology-based screening program for cervical cancer in 1999 as part of its National Cancer Control Policy (NDoH, 1999). The goal of the cytology-based screening program was to screen 70% of the target population within ten years of implementation. Study II described cervical cancer screening program trends based on routinely collected health service data for women 30 years and older reported by health sub-district and year. Among the findings of this study is the high cervical cancer incidence rates, with a considerable proportion of women presenting at an advanced

stage of the disease. These findings may indicate a low reach of screening in this area which is below the initial goal of the screening program; a minimum of 70% women coverage over ten years. Based on these results, recipients of this screening program benefited extraordinarily little, although this program was rolled out more than 20 years ago. Some of the disappointing results may be associated with several studies whose meta-analyses suggested that cytological screening has a low sensitivity of 47% while specificity is just above 60% (Fahey et al., 1995; Nanda et al., 2000). Assuming that cytology is only moderately sensitive, high coverage with frequent repeats may have contributed to the decline in the risk of cervical cancer in developed countries. With many barriers highlighted, including low screening frequency in South Africa, there is still a lot needed to reduce both morbidity and mortality due to this disease. These findings provide crucial information on the implementation evaluation of this national program and are a statistical infrastructure for health to the South African government.

The primary health care system in South Africa is available; however, limited resources negatively affect the deliverance of its services. Many people still have to be referred to hospitals for better treatment services. Some women have access to a primary healthcare facility for screening, but there is a delay in the referral to the next level of care due to financial and transport challenges.

In conclusion, the declines in cervical cancer rates and reduced death; about 20% to 60% in developed countries are beneficial effects of population-based cytology screening programs (Fisher & Brundage, 2009; H. Hakama et al., 1986; M. Hakama et al., 1985; Miller et al., 1990; Saslow et al., 2002). Even though South Africa started with the national cytology screening to women almost 20 years ago, morbidity and mortality due to cervical cancer are still high. The main problem identified is a lack of awareness about the program experience, translating to limited population coverage (Ramathuba et al., 2016). The added issue of fragmented services with little or no follow-up for women with positive smears is still a challenge (Cronje & Beyer, 2007; Mosavel et al., 2009; Sibiya & Grainger, 2007). The systematic challenge and unequal distribution of resources compounded in the rural clinics is still an obstacle to the envisaged progress (Sibiya & Grainger, 2007). Other factors that determine economic and social status are also important, including poor or limited education and training with low-income levels and high parity. Several studies also reported an excess relative risk for cervical cancer in these women (Pukkala & Weiderpass, 1999; Weiderpass et al., 2000).

Eastern Cape Province suffers a brain drain and is one of the provinces contributing to migrant work. In the migrant labor work system, men leave home for a year or longer to work in cities, mainly with mines, where they are at risk of having multiple partners, and this later adds to the burden. It is one of the poorer provinces in the Republic of South Africa. Consistent with this, men's life expectancy in the Eastern Cape is 62.5

years versus 68.5 its women (StatsSA, 2020). Because of these factors, women become breadwinners in most rural communities in the Eastern Cape Province. It thus cannot be overstated that a change in one woman's life can have a notable difference in the reduction in the risk of dying due to cervical cancer.

The WHO (2018) defines population screening as the plausible identification of unrecognized disease in a supposedly healthy population with tests, examination, or other procedures that can be applied rapidly to and efficiently in the target population. Screening is a process that begins with an invitation to take part and ends with treatment for appropriately identified individuals. An effective screening program must include all core components such as availability of suitable tests or examinations with high-level adequacy, a test that is acceptable to the population, an agreed-upon policy on who to treat as patients, availability of facilities for diagnosis and treatment, and the cost of screening. The screening process must benefit the population economically than just an item of expenditure on medical care. Ideally, a comprehensive approach with the continuing operation is more beneficial to program recipients than a "once-off project" (WHO, 2002). The complete system includes social mobilization through health education programs on risk factors and health promotion, primary prevention through screening the high-risk population for early diagnosis, and access to treatment (Vineis & Wild, 2014; WHO, 2017). The more organized screening program includes invitations of qualifying women as prescribed by the screening policy. A call/recall system based on personal invitations is vital for an organized program. It is mainly practiced in Europe. For this purpose, preparations for the program include creating a correct list of the target population with names and addresses. It is essential to monitor simple basics. Results must be observed and are simple basics that reduced more than 50% cervical cancer incidence and mortality in countries like Finland (Anttila & Nieminen, 2000).

There is no doubt that cervical cancer has a known natural history and is adequately well studied. The population in the Eastern Cape Province is a significant public health problem. The rate at which these women die challenges the country's economy. Also, women's participation in the current free cytology-based screening program is lower than expected. Therefore, the status quo requires innovative ways to overcome the high morbidity and mortality rates of cervical cancer. Screening is a cost-effective cervical cancer control strategy with proven effectiveness. Organized cytology-based screening programs achieved high coverage rates, and the treatment of pre-cancerous lesions led to significant reductions in cervical cancer incidence and mortality.

The National Health Department of South Africa must review the current policy on cervical cancer screening, including proper planning, monitoring, and evaluation of the program. In addition to the recent cytology-based screening, other screening methods

combined with relatively simple, safe, and effective outpatient methods for treating pre-cancer lesions such as cryotherapy or loop electrosurgical excision procedure (LEEP) may be considered. Others include the visual inspection with acetic acid (VIA), visual inspection with Lugol's iodine (VILI), and Human Papillomavirus (HPV) DNA testing. However, each method has strengths and limitations that need to be considered in the national policy when choosing the proper screening method. Essential and most important is the political will and commitment, leadership, and good stewardship of the South African health system.

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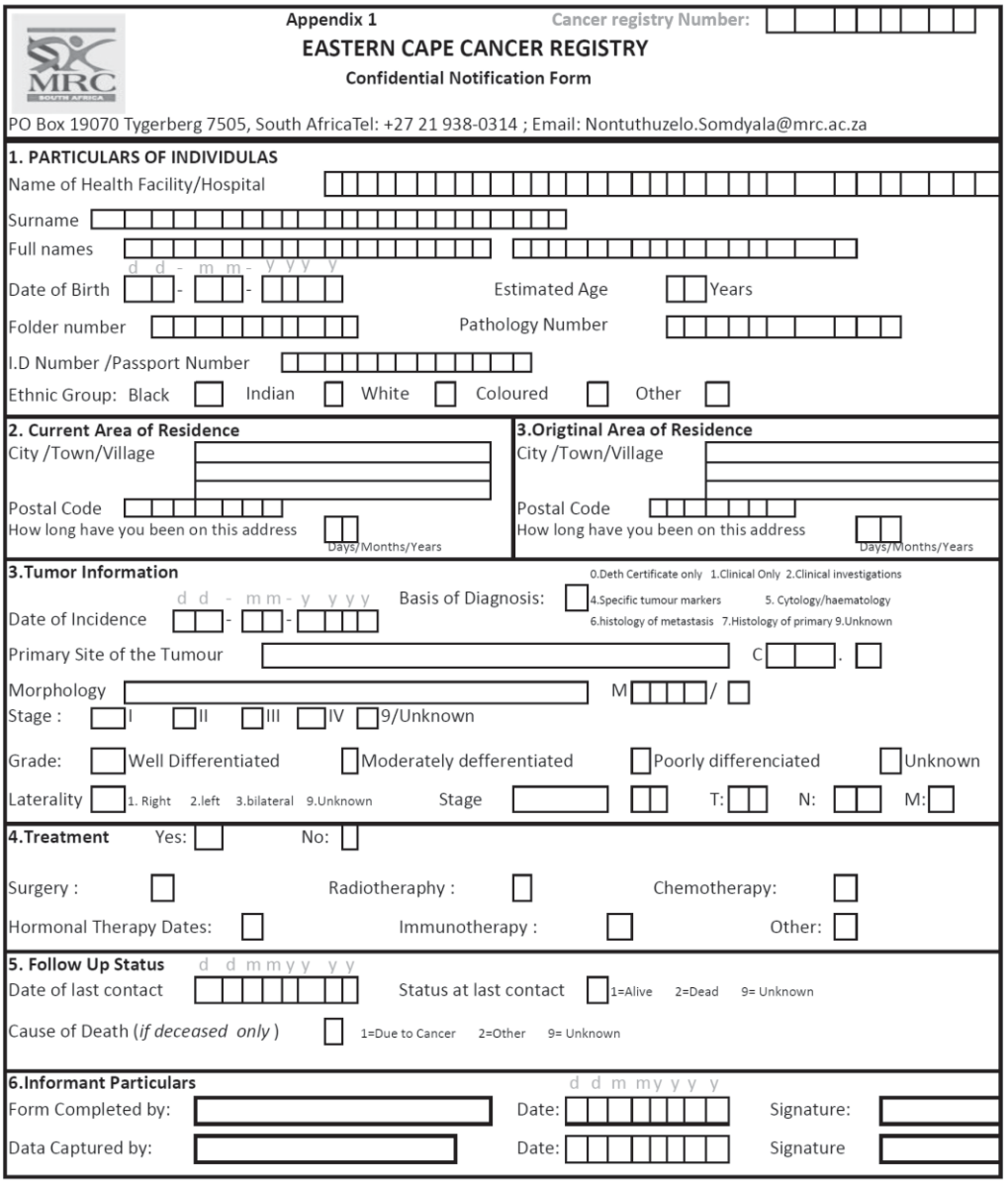
APPENDICES

Appendix 1: CONFIDENTIAL NOTIFICATION FORM



Appendix 1 Cancer registry Number:

EASTERN CAPE CANCER REGISTRY

Confidential Notification Form

PO Box 19070 Tygerberg 7505, South AfricaTel: +27 21 938-0314 ; Email: Nontuthuzelo.Somdyala@mrc.ac.za

1. PARTICULARS OF INDIVIDULAS

Name of Health Facility/Hospital

Surname

Full names

Date of Birth (d d - m m - y y y y) Estimated Age Years

Folder number Pathology Number

I.D Number /Passport Number

Ethnic Group: Black Indian White Coloured Other

2. Current Area of Residence

City /Town/Village

Postal Code

How long have you been on this address Days/Months/Years

3.Origtinal Area of Residence

City /Town/Village

Postal Code

How long have you been on this address Days/Months/Years

3.Tumor Information

Date of Incidence (d d - m m - y y y y) Basis of Diagnosis: 0.Deth Certificate only 1.Clinical Only 2.Clinical investigations 4.Specific tumour markers 5. Cytology/haematology 6.histology of metastasis 7.Histology of primary 9.Unknown

Primary Site of the Tumour C .

Morphology M /

Stage : I II III IV 9/Unknown

Grade: Well Differentiated Moderately defferentiated Poorly differenciated Unknown

Laterality 1. Right 2.left 3.bilateral 9.Unknown Stage T: N: M:

4.Treatment Yes: No:

Surgery : Radiotheraphy : Chemotherapy:

Hormonal Therapy Dates: Immunotherapy : Other:

5. Follow Up Status (d d m m y y y y)

Date of last contact Status at last contact 1=Alive 2=Dead 9= Unknown

Cause of Death (*if deceased only*) 1=Due to Cancer 2=Other 9= Unknown

6.Informant Particulars (d d m m y y y y)

Form Completed by: Date: Signature:

Data Captured by: Date: Signature

I

Cancer incidence in a rural population of South Africa, 1998–2002

Somdyala, NIM., Bradshaw, D., Gelderblom, WCA., Parkin, DM.

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global cancer control

IJC
International Journal of Cancer

Cancer incidence in a rural population of South Africa, 1998–2002

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Cancer incidence rates and patterns are reported for a rural population, living in the Eastern Cape Province of South Africa for the period 1998–2002. The population-based cancer registry has operated for 20 years, using both active and passive methods for case finding, through collaborations with 19 health facilities: 11 district hospitals, 7 referral hospitals and 1 regional laboratory. The age standardized incidence rates for all cancers were 73.1 per 100,000 in males and 64.1 per 100,000 in females. The leading top 5 cancers for males were oesophagus (32.7 per 100,000), lung (5.8 per 100,000), prostate (4.4 per 100,000), liver (4.4 per 100,000) and larynx (2.5 per 100,000) whereas for females they were cervix (21.7 per 100,000), oesophagus (20.2 per 100,000), breast (7.5 per 100,000), ovary (0.9 per 100,000) and liver (0.9 per 100,000). The incidence of Kaposi sarcoma was low, and higher for males (1.6 per 100,000) than females (0.3 per 100,000). Lung cancer in both males and females was relatively low compared to the high incidence of oesophagus cancer.

Information about disease burden is important for monitoring the health of the nation. In South Africa, a middle income country, such information, including cancer incidence and mortality data, is relatively sparse. A national pathology-based cancer register, established in 1986, has provided limited information on the cancer burden based on voluntary reporting by pathology laboratories of invasive cancers diagnosed by histology, cytology or haematology.[1] However, the registry has been unable to provide a complete measure of the incidence of cancers, and has not reported since 1999.[2] In a country such as South Africa, with a diversity of cultures and living conditions, population-based cancer registries monitoring the incidence in different settings become very important. The need to strengthen the national cancer register as well as developing population-based registries in a variety of settings has been identified in the context of developing a National Cancer Control Programme.

Over 20 years ago, the Medical Research Council (MRC) of South Africa established a population-based cancer register in 4 magisterial areas of the former Transkei area of the Eastern Cape Province. The original purpose was to monitor geographic and temporal variations in the incidence of oesophageal cancer, which was known to be particularly common in this area.[3,4] The register has developed to include all cancers and in 1998 was extended to include 10 magisterial areas covering the areas of Butterworth, Centane (Kentani), Idutywa, Nqamakwe, and Willowvale in the South West, and Bizana, Flagstaff, Lusikisiki, Port St Johns, and Umzimkulu in the North East. These districts now comprise 7 local municipalities (Fig. 1). The population at the most recent census in 2001 was 1.3 million.[5] This register is independent of the pathology based national cancer register which has limited geographic information.

The majority of inhabitants of this area are indigenous (black) Africans who speak isiXhosa and support both Christian and traditional norms and values. The demography in these rural magisterial areas is typical of a developing country with about 43% of the population under 15 years of age.[5] The average life expectancy for the province has been estimated to have dropped to 48 years as a result of the AIDS epidemic.[6] The population is generally poor and the unemployment rate is 27%.[5] Family members seek employment in the urban areas including the gold mines in Gauteng and the Free State Provinces, and coal mines in the KwaZulu-Natal Province. Subsistence farming is widely practiced.

This article reports cancer incidence for the rural population of South Africa, living in 8 magisterial areas of the former Transkei region of the Eastern Cape Province, for the period 1998–2002. The areas include Butterworth, Centane (Kentani), Idutywa, Nqamakwe, and Willowvale in the South West, and Bizana, Flagstaff, Lusikisiki in the North East. The other 2 areas are not reported due to data quality concerns. This study will form a baseline for the newly extended surveillance area.

Key words: cancer incidence, rural population, South Africa, population-based registry
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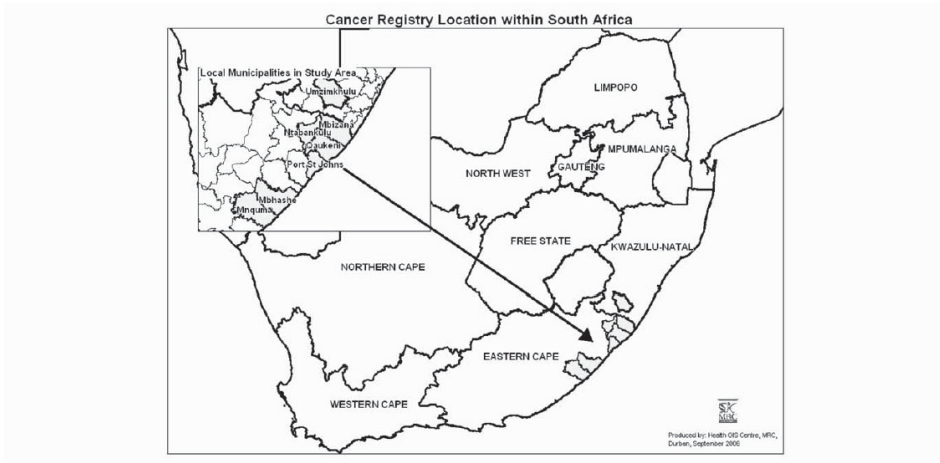

Figure 1. Map of cancer registration area within South Africa. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Materials and Methods

Cancer care facilities

The public healthcare delivery system is based on a network of primary healthcare clinics, healthcare centers, district hospitals and referral hospitals provided by the government. Basic laboratory services are available in most public healthcare centers. Patients suspected to have cancer in the primary and secondary care facilities are mostly referred to Mthatha General Hospital Complex that serves as a central referral hospital for the region, where the regional state laboratory, the Nelson Mandela Pathology Laboratory, is also located. For specialized services including oncology and radiotherapy, patients are referred to hospitals such as Inkosi Albert Luthuli (oncology services since 2003), King George V (with specialist thoracic-surgery), King Edward VIII, and Addington hospitals in Durban, KwaZulu-Natal Province, and Frere (with radiation and oncology services) and Cecilia Makiwane hospitals in East London, Eastern Cape Province. The government provides transport to send cancer patients to these hospitals. However, patients must travel between 200 and 700 kilometers to get these specialized services and care.

South Africa has a private health sector incorporating medical practitioners, hospitals and laboratory services that caters for ~20% of the South African population who can afford such care or/and have health insurance. The registry does not have access to data from these facilities. However, there are no private hospitals in the area and the proportion of this study population who use private care would be extremely small.

Case finding

The registry collaborates with all hospitals in the surveillance area as well as the major public sector centers to the north and south of it, to which patients from the area would be expected to be referred. In total, 19 hospitals (11 district, 7 referral and a regional laboratory under the National Health Laboratory Services (NHLS) collaborate with the registry. Both active and passive methods are used for case finding based on the hospital's recorded residential address of cancer patients. The active case finding system involves annual visits to the collaborating hospitals with field trips twice a year. Active case finding extends to all of the referral hospitals outside the registration area described above. Passive case finding is undertaken by part-time oncology nurses who complete specially designed cancer notification forms and send them to the registry on a monthly basis. The nurses were trained in cancer data abstraction by the registry manager. Death certificates are not used as source of information as many deaths occurring in the registry area are not medically certified.

Data were manually abstracted from the records and included demographic variables, tumor characteristics including the site, type and behavior. Cancer sites were manually coded in the registry for topography and morphology according to the third edition of the International Classification of Diseases for Oncology (ICD-O)[7] and captured using the latest version of CanReg,[8] a customized software computer program designed by the Unit of Descriptive Epidemiology of the International Agency for Research on Cancer (IARC) for cancer registration.

Population

The 2001 census was used to estimate population at risk in 1998–2002. More than 97% of the population are Xhosa speaking black Africans. The age and sex distribution of the

Epidemiology

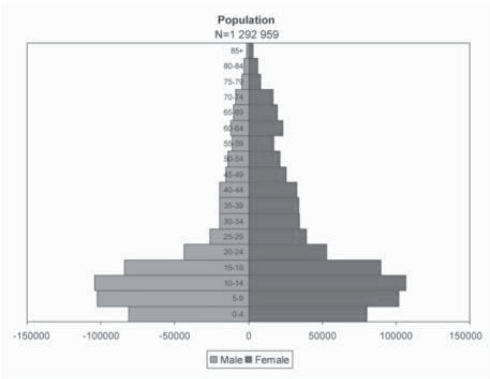

Figure 2. Age distribution of population, 2001. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

population, shown in Figure 2, is typical of a South African rural population. It reflects that the area is a labor reservoir, in which there are more children and older persons, particularly women, than there are working age adults, especially males. Labor migration is historically significant in South Africa. Such a migratory pattern may result in a lower cancer incidence being experienced in the area as it is possible that people from this area that develop a cancer while working in an urban area, do not return to their rural home. On the other hand, some patients diagnosed elsewhere might return home to die and would inflate the incidence rate if they had not been counted in area at the time of the census. However, this is likely to have a limited effect as only those patients who receive treatment at the collaborating health facilities are included in the register. The number of children under 5 years of age is markedly smaller than the next age group. This is likely to be a result of declining fertility on the one hand and under-enumeration of young children on the other.

Data analysis

Data for the period 1998–2002 were cleaned, and a search made for duplicate records based on name, age, sex and diagnosis. Validity checks identified impossible codes and unlikely combinations. Only malignant cases were included in the analysis; cases from outside the registration area were excluded. The number of incident cases is presented by age, sex and site as well as method of diagnosis. Incidence rates were estimated, as well as the registration area as a whole, as age specific, crude and age standardized rates (using World Standard Population).

Results

A total of 2,501 new cancer cases were reported for the period 1998–2002. There were 1,022 (40.9%) males and 1,479 (59.1%) females. The annual number of cases was fairly consistent during this period with an annual average of 500 per annum (204 males and 295 females). The numbers in 1999 and 2000, however, were lower than average (452 and 430, respectively). The average age at diagnosis was 56.2 years with the majority of cases in the age range 50–74 years. A total of 1,172 cases had a laboratory report, of which 981 also had a hospital report. A total of 2,301 cases had a hospital report, with hospitals in the registration area contributing 1,473 cases (64.0%) and the referral hospitals, including the state pathology laboratory, contributing 1,032 cases (44.9%) (204 cases were notified from both sources). Frere Hospital, which is the only radiation and oncology center in the region, accounted for 593 cases. With 1,329 cases notified from hospital records only, 191 from laboratory reports only, and 981 from both sources, the maximum likelihood estimate of the number of cases missed (not reported from either) is 259, indicating a completeness of case ascertainment of 90.6% (95% CI 89.5–91.7%).

Tables 1 and 2 show the number of reported cancers by primary site, age group, and sex, together with the percentage frequency, crude and age standardized incidence rates. Figure 3 shows the ranking of the 10 cancers with the highest age-standardized incidence rates, by sex. In males, the most frequently reported cancers were oesophageal (43.4%, ASR 32.7 per 100,000), lung (7.2%, ASR 5.8 per 100,000), prostate (6.8%, ASR 4.4 per 100,000) and liver (6.1%, ASR 4.4 per 100,000). In females, the most common cancers were cervix (33.2%, ASR 21.7 per 100,0000), oesophageal (32.4%, ASR 20.2 per 100,000) and breast (11.0%, ASR 7.5 per 100,000). There were relatively few Kaposi sarcoma cases, in both males (2.1%, ASR 1.6 per 100,000) and females 0.5%, ASR 0.3 per 100,000). Cases 1,130 (45.2%) had been diagnosed on the basis of clinical information only including X-ray and biochemical/biological tests without histological confirmation whereas 54.8% were cases with histological or cytological confirmed diagnosis. Out of the total of 923 oesophageal cancer cases, 115 (12.5%) had histological confirmation of diagnosis. Of these cases (87.6%) were squamous cell carcinomas and only one case (0.8%) adenocarcinoma; 13 cases (11.5%) had a nonspecific histological diagnosis (e.g., carcinoma NOS).

Figure 4 shows the age specific incidence rates for the most common cancers. The incidence of cancer of the oesophagus increases steadily with age to reach a maximum at age 65–69, although the rates in females are lower at all ages. Lung cancer incidence rates in males increase markedly from age 35–39 reaching a peak at 55–59, whereas in females, the rates are 10-fold lower. Prostate cancer is confined to ages over 50, and rates increase steadily with age. Cervix cancer incidence rates increase to a peak at ages 60–64; in contrast, breast cancer incidence rates are lower and become relatively constant after ages 40–44.

There were 73 childhood cancers in total which accounted for 2.8% of all the cancers reported during the 1998–2002 period. The most common childhood cancers observed were nephroblastoma (15 cases), brain tumours (15 cases),

Table 1. Incident cases by age and sex and annual incidence rates (crude and age-standardised) by site, 1988–2002

	0–14	15–24	25–34	35–44	45–54	55–64	65–74	75+	All ages	% of Total	HV%	Crude rate	ASR	ICD 10
a. Males														
Lip	0	0	0	2	0	0	0	0	2	0.2	100.0	0.1	0.2	C00
Tongue	0	0	0	2	5	10	8	4	29	2.8	86.2	1.2	2.1	C01-C02
Mouth	0	0	0	3	7	9	7	4	30	2.9	70.0	1.3	2.3	C03-C06
Salivary glands	0	1	0	0	1	0	0	0	2	0.2	100.0	0.1	0.1	C07-C08
Tensil	0	0	0	0	1	2	3	1	7	0.7	100.0	0.3	0.5	C09
Nasopharynx	0	0	0	0	1	0	0	0	1	0.1	100.0	0.0	0.1	C11
Hypopharynx	0	0	0	0	1	0	1	0	2	0.2	100.0	0.1	0.2	C12-C13
Pharynx unspec.	0	0	0	0	0	4	0	0	4	0.4	100.0	0.2	0.3	C14
Oesophagus	0	0	2	24	80	128	166	44	444	43.4	16.2	18.9	32.7	C15
Stomach	0	0	3	2	6	3	5	2	21	2.1	38.1	0.9	1.6	C16
Small intestine	0	0	0	0	0	1	0	0	1	0.1	100.0	0.0	0.1	C17
Colon	0	2	2	3	3	2	4	1	17	1.7	70.6	0.7	1.2	C18
Rectum	0	0	1	1	1	1	4	1	9	0.9	55.6	0.4	0.6	C19-C20
Anus	0	0	0	1	0	0	0	0	1	0.1	100.0	0.0	0.1	C21
Liver	3	3	4	7	19	5	13	8	62	6.1	6.5	2.6	4.4	C22
Gallbladder etc.	0	0	0	0	0	1	0	0	1	0.1	0.0	0.0	0.1	C23-C24
Pancreas	0	0	1	0	3	2	2	1	9	0.9	11.1	0.4	0.7	C25
Larynx	0	0	0	0	6	12	10	6	34	3.3	88.2	1.4	2.5	C32
Trachea bronchus lung	0	2	0	6	19	26	19	2	74	7.2	67.6	3.1	5.8	C33-C34
Bone	2	1	0	2	2	2	2	0	11	1.1	100.0	0.5	0.7	C40-C41
Melanoma of skin	0	1	0	2	2	3	2	0	10	1.0	80.0	0.4	0.8	C43
Other skin	0	0	0	0	1	3	5	0	9	0.9	77.8	0.4	0.6	C44
Mesothelioma	0	1	0	0	2	0	0	0	3	0.3	100.0	0.1	0.2	C45
Kaposi sarcoma	0	2	4	8	5	1	0	1	21	2.1	10.0	0.9	1.6	C46
Connective soft tissue	2	3	0	0	1	5	2	0	13	1.3	100.0	0.6	0.8	C47;C49
Breast	0	0	0	0	0	0	3	2	5	0.5	100.0	0.2	0.3	C50
Penis	0	0	1	1	1	1	0	2	6	0.6	100.0	0.3	0.4	C60
Prostate	0	0	0	0	2	16	28	23	69	6.8	28.0	2.9	4.4	C61
Testis	0	0	1	0	0	0	2	0	3	0.3	100.0	0.1	0.2	C62
Kidney	13	0	0	2	1	0	1	0	17	1.7	29.4	0.7	0.7	C64
Bladder	0	0	0	0	2	0	5	2	9	0.9	55.6	0.4	0.6	C67
Eye	3	0	0	1	1	1	0	0	6	0.6	50.0	0.3	0.3	C69
Brain, nervous system	5	1	0	1	1	0	1	0	9	0.9	100.0	0.4	0.4	C70-C72
Thyroid	0	0	0	1	0	1	3	0	5	0.5	40.0	0.2	0.3	C73
Hodgkin disease	0	1	0	0	2	2	0	0	5	0.5	100.0	0.2	0.4	C81-C82
Non-Hodgkin lymphoma	1	1	0	1	1	1	0	0	5	0.5	60.0	0.2	0.3	C85;C96
Multiple myeloma	0	0	0	1	3	8	4	0	16	1.6	50.0	0.7	1.3	C90
Lymphoid Leukaemia	3	0	0	0	0	0	0	0	3	0.3	100.0	0.1	0.1	C91
Myeloid leukaemia	0	0	0	1	0	0	1	0	2	0.2	100.0	0.1	0.1	C92-C94
leukaemia unspec.	4	0	0	0	0	0	0	0	4	0.4	100.0	0.2	0.1	C95

Table 1. Incident cases by age and sex and annual incidence rates (crude and age-standardised) by site, 1988–2002 (Continued)

	0–14	15–24	25–34	35–44	45–54	55–64	65–74	75+	All ages	% of Total	HV%	Crude rate	ASR	ICD 10
Other and unspecified	2	1	1	3	7	12	12	3	41	4.0	0.0	1.7	2.9	Other
All sites Total	38	20	20	75	187	262	313	107	1022	100.0	36.6	43.4	73.1	
All sites but C44	38	20	20	75	186	259	308	107	1013	99.1	37.0	43.0	72.4	
b. Females														
Lip	0	0	0	1	0	1	1	0	3	0.2	100.0	0.1	0.1	C00
Tongue	0	0	0	0	0	0	2	1	3	0.2	33.3	0.1	0.1	C01-C02
Mouth	0	1	1	1	0	0	7	2	12	0.8	91.7	0.4	0.4	C03-C06
Salivary glands	1	1	0	0	0	1	1	0	4	0.3	75.0	0.1	0.1	C07-C08
Tensil	0	0	0	1	1	0	0	1	3	0.2	2.0	0.1	0.1	C09
Other oropharynx	0	0	0	1	0	1	0	0	2	0.1	100.0	0.1	0.1	C10
Nasopharynx	0	0	1	0	1	0	0	1	3	0.2	66.7	0.1	0.1	C11
Pharynx unspec.	0	0	0	1	0	0	1	0	2	0.1	100.0	0.1	0.1	C14
Oesophagus	0	1	4	24	72	170	165	43	479	32.4	9.0	16.6	20.2	C15
Stomach	0	0	0	3	1	6	1	1	12	0.8	0.7	0.4	0.5	C16
Small intestine	0	0	1	0	0	0	0	0	1	0.1	100.0	0	0.1	C17
Colon	0	0	1	0	2	4	2	0	9	0.6	55.6	0.3	0.4	C18
Rectum	0	0	1	1	1	3	1	0	7	0.5	14.3	0.2	0.3	C19-C20
Anus	0	0	0	1	0	2	1	0	4	0.3	100.0	0.1	0.2	C21
Liver	0	1	0	5	4	5	3	2	20	1.4	15.0	0.7	0.9	C22
Gallbladder etc.	0	0	0	0	1	0	2	0	3	0.2	33.3	0.1	0.1	C23-C24
Pancreas	0	0	0	1	4	6	2	0	13	0.9	7.7	0.5	0.6	C25
Nose. Sinuses etc.	0	1	0	0	1	0	0	1	3	0.2	100.0	0.1	0.1	C30-C31
Larynx	0	0	0	0	2	3	0	0	5	0.3	80.0	0.2	0.3	C32
Traohea, bronchus, lung	0	0	0	2	5	6	5	0	18	1.2	61.1	0.6	0.8	C33-C34
Bone	1	1	0	2	3	2	1	0	10	0.7	100.0	0.3	0.4	C40-C41
Melanoma of skin	0	0	0	1	3	6	4	1	15	1.0	88.1	0.5	0.7	C43
Other skin	0	0	1	2	0	3	4	0	10	0.7	92.2	0.3	0.4	C44
Kaposi sarcoma	0	2	2	1	2	0	0	0	7	0.5	42.9	0.2	0.3	C46
Connective. soft tissue	1	1	2	1	2	0	1	0	8	0.5	100.0	0.3	0.4	C47;C49
Breast	0	1	8	38	42	35	29	9	162	11.0	74.7	5.6	7.5	C50
Vulva	0	0	0	0	1	0	1	0	2	0.1	100.0	0.1	0.1	C51
Vagina	0	0	0	0	1	1	0	0	2	0.1	100.0	0.1	0.1	C52
Cervix uteri	0	2	28	68	107	133	117	36	491	33.2	72.9	17.1	21.7	C53
Corpus uteri	0	0	0	2	7	4	8	0	21	1.4	76.2	0.7	0.9	C54
Uterus unspec.	0	0	0	4	1	5	3	2	15	1.0	40.0	0.5	0.6	C55
Ovary	1	0	2	1	4	9	3	0	20	1.4	85.0	0.7	0.9	C56
Placenta	0	2	3	2	1	0	0	0	8	0.5	25.0	0.3	0.4	C58
Kidney	3	0	0	0	0	1	0	0	4	0.3	25.0	0.1	0.1	C64
Bladder	0	0	0	1	0	2	3	1	7	0.5	85.7	0.2	0.3	C67
Other urinary organs	0	0	0	1	0	0	0	0	1	0.1	100.0	0	0	C68

Table 1. Incident cases by age and sex and annual incidence rates (crude and age-standardised) by site, 1988–2002 (Continued)

	0–14	15–24	25–34	35–44	45–54	55–64	65–74	75+	All ages	% of Total	HV%	Crude rate	ASR	ICD 10
Eye	7	0	2	0	0	0	2	0	11	0.7	63.6	0.4	0.4	C69
Brain nervous system	10	2	1	1	0	1	1	0	16	1.1	100.0	0.6	0.5	C70-C72
Thyroid	0	0	2	3	5	4	0	1	15	1.0	46.7	0.5	0.7	C73
Adrenal gland	1	0	0	0	0	0	0	0	1	0.1	100.0	0	0	C74
Hodgkin disease	2	0	0	0	0	0	0	0	2	0.1	100.0	0.1	0	C81
Non–hodgkin lymphoma	0	2	1	2	2	0	0	0	7	0.5	85.1	0.2	0.3	C82-C85; C96
Multiple myeloma	0	0	0	0	1	3	1	1	6	0.4	50.0	0.2	0.3	C90
Lymphoid leukaemia	2	0	0	0	0	0	0	0	2	0.1	100.0	0.1	0	C91
Myoloid leukaemia	1	0	1	0	1	1	0	0	4	0.3	100.0	0.1	0.2	C92-C94
Leukaemia unspec.	5	2	0	0	0	0	0	0	7	0.5	57.1	0.2	0.2	C95
Other and unspecified	0	0	1	2	2	7	5	2	19	1.3	0.0	0.7	0.8	Other
All sites Total	35	20	63	174	280	425	377	105	1479	100.0	48.9	51.4	64.1	
All sites but C44	35	20	62	172	280	422	373	105	1469	99.3	49.2	51.0	63.7	

HV–Histologically verified, ASR–Age standaridised rate

leukemia (14 cases), and retinoblastoma (11 cases) and neuroblastoma (10 cases).

Discussion

The overall age standardized incidence per 100,000 population for cancer (excluding non-melanoma skin cancer) was 72.4 for males and 63.7 for females respectively. These rates appear low, but there are few data from rural populations in low income countries with which they can be compared. They are similar to the rates reported from Gambia in 1997–98[9] and rates from the rural population of Barshi in India in 1988–92.[9] The common cancers observed during this period were oesophagus, cervix, breast, lung, prostate and liver, and the ranking was largely dominated by oesophageal and cervical cancers. Table 2 compares the rates in the Eastern Cape (this study) with those recorded by the National Cancer Registry (histological diagnosed cases)[1] and by the cancer registry of Swaziland in 1996–99.[10] It can be seen that the pattern in this area is distinct.

Oesophageal cancer incidence rates for this region are higher than those observed elsewhere in Africa[10] or for the Black population in the USA.[11] Oesophageal cancer incidence rates for this region have been consistently high for a period of more than 50 years,[3,4,12–15] despite a low frequency of histological confirmation; diagnosis is generally clinical with confirmation by radiology (barium swallow), since few cases receive any definitive treatment. Oesophageal cancer is related to tobacco smoking and alcohol drinking, and the difference in rates between males and females is consistent with the different prevalence of use of tobacco and alcohol, although neither habit is common in the local population. Results from a household survey conducted during 2002 by the Eastern Cape Department of Health (Bisho, South Africa)[16] and Equity Project indicated that in the former Transkei region 16% of men drink alcohol regularly while 13% partake in communal drinking. The prevalence is much lower among women with only 4% drinking regularly and another 4% partaking in communal drinking. This survey also found that 31% of men smoke tobacco and only 5% women, although even in men, daily consumption is modest (3.2 cigarettes per day). Dietary deficiencies and fungal toxins are some of the other risk factors that have been thought to be associated with the development of oesophageal cancer in this region.[17,18] Many early studies were concerned with the geographical differences in incidence within the former Transkei, and a possible correlation with exposure to fumonisins from moldy maize.[18] However, an association between exposure to fumonisins and individual risk of oesophageal cancer has not been demonstrated.[19]

Cervical cancer was the most common cancer among women reported in this region with an ASR of 21.7 per 100,000, about 3 times higher than that of breast cancer. The incidence is, however, lower than that recorded in South Africa as a whole (Table 2).[1] Cervix cancer is classified as an AIDS-defining cancer, although the risk of invasive cervical cancer in Africa seems little influenced by HIV, and trends do not reflect changing prevalence of infection.[20] Rather, incidence is related to prevalence of infection with Human Papillomavirus (HPV), modified by the protective effect of screening. South Africa has adopted a national policy of

Table 2. Age standardised incidence rates: Eastern Cape (1998–2002), National Cancer Registry of South Africa (1999)[1] and Swaziland cancer registry (1996–1999)[10]

Cancer site	Eastern Cape (1998–2002)	South Africa, Black (1999)	Swaziland (1996–99)
Male			
Oesophagus	32.7	14.1	14.0
Stomach	1.6	3.6*	4.5
Colon and rectum	1.8	3.0	4.2
Liver	4.4	2.6	2.2
Larynx	2.5	4.1	4.5
Lung	5.8	9.3	10.1
Prostate	4.4	17.2	21.5
Kaposi sarcoma	1.6	2.8	17.2
Non-Hodgkin lymphoma	0.3	2.2	3.3
All Sites	73.1	97.1	145.3
Female			
Oesophagus	20.2	7.0	4.1
Liver	0.9	1.3	5.2
Breast	7.5	18.4	12.1
Cervix	21.7	34.9	59.3
Uterus	0.6	4.7	5.6
Ovary	0.9	2.8	3.2
Kaposi sarcoma	0.3	1.5	9.5
Non-Hodgkin lymphoma	0.3	1.5	1.7
All Sites	64.1	103.7	134.8

*1998

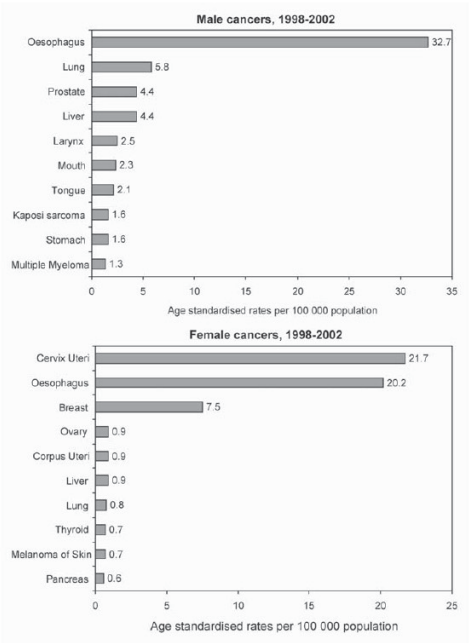

Figure 3. Age standardized incidence rates per 100,000 by sex, 1998–2002. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

offering, a free screen to asymptomatic women aged 30 years, followed by 2 further screens 10 years apart. Reviews of the programme suggest major challenges in implementation, however, even in the more resourced areas of the country.[21,22] While in the long-term vaccination against the HPV will provide effective prevention, implementation will require careful community preparation, and, in any case, secondary prevention through screening urgently needs to be strengthened for the current generation of women. Although studies in South Africa have shown the feasibility of screening using visual inspection with acetic acid (VIA)[23] current evidence suggest that the preferred screening option will involve inexpensive tests for HPV.[24] The registry has an important role to play in monitoring trends in cervical cancer incidence in the context of the HIV/AIDS epidemic on the one hand and the possible improvements in cervical cancer prevention on the other.

Breast cancer accounted for 11.0% of cancers with ASR of 7.5 per 100,000, somewhat lower than the rate recorded nationally (Table 2). The incidence rates peak as early as age 40–44 and remain at a similar level across older ages whereas in South Africa peak incidence occurs at ages 55 and above.[1] This may reflect increasing rates in younger generations of women in the Eastern Cape region.

The estimated completeness of case ascertainment, based on capture–recapture by the 2 sources used (hospital notifications and pathology records), is 90.6%. This estimate depends on the assumption of independence of the 2 sources (that detection by each source is independent of the other).[25] It may be something of an overestimate, in fact, if there is positive dependence (more likelihood of being notified from hospital if there is a laboratory report, for example), but we have no means of evaluating any possible bias in the estimate. Despite this reasonably high level of ascertainment from the data sources covered, it is possible that under-diagnosis of cases may be an issue in this rural population, with difficulties in accessing medical services. For example, the lung cancer rates in this region are low when compared with the national figures (Table 2)[1] and much lower than rates in other southern African centre of Harare in Zimbabwe (17.4 per 100,000).[26] However, low rates have also been reported by registries in West African countries such as Mali (2.7 per 100,000) and Uganda (3.9 per 100,000),[27] and may simply be the consequence of low prevalence and intensity of tobacco smoking, rather than a

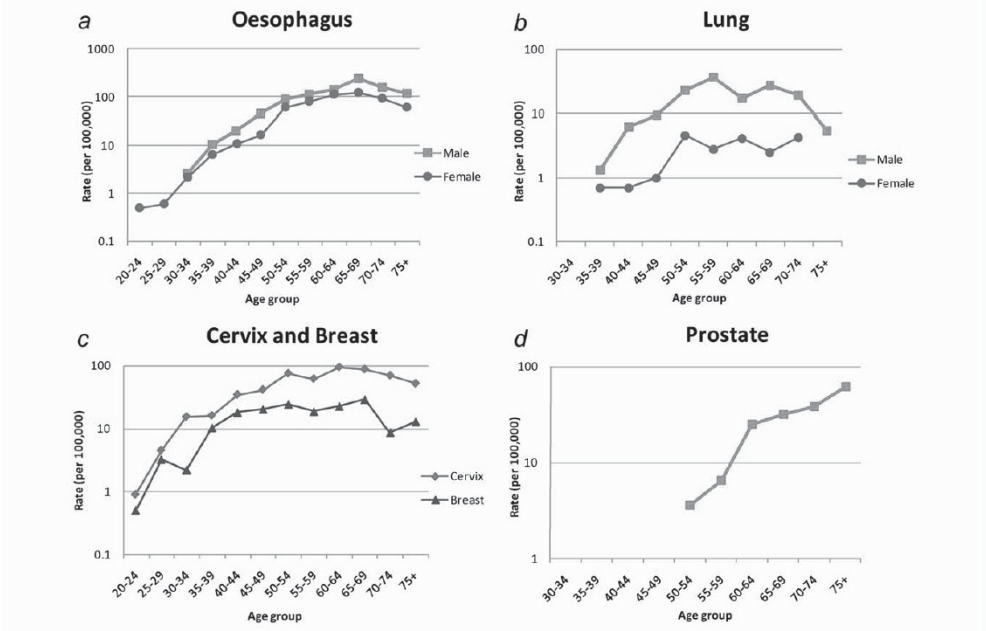

Figure 4. Age specific incidence rates (log scales) for selected cancers, 1998–2002. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

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failure of diagnosis or registration. In contrast, the incidence of liver cancer in this region is very low (ASR in males 4.4 per 100,000 and 0.9 per 100,000 in females) compared to national and Swaziland rates (Table 2) and Harare (14.4 and 12.7 per 100,000 in men and women respectively, in 1998–2002).[26] Prevalence of hepatitis B infection in South Africa was considered to be endemic prior to the introduction of a vaccination in 1995. Robson and Kirsh reported the prevalence among black South Africans to be around 8%.[28] Although there is no population based data, the prevalence was probably also relatively high in the study population. The low liver cancer incidence rates observed in this study may therefore represent under-diagnosis of a cancer for which hospitalization rates may be rather low. Similarly, the high proportion of some cancers diagnosed by histology, such as brain and nervous system, suggests that limited access to noninvasive diagnostic technology may also result in under-diagnosis of cases. Without including information from death certificates, the more lethal cancers may well be under represented.

Kaposi sarcoma accounted for only 2.1% of male cancers and 0.5% of female cancers during 1998–2002. This was unexpected given the rapidly growing prevalence of HIV in South Africa,[29] as well as the clear association of Kaposi sarcoma with HIV.[30] ASRs per 100,000 of 1.6 in males and 0.3 in females for Kaposi sarcoma were very low when compared with other African countries with a high HIV prevalence. Kaposi sarcoma is only a common manifestation of HIV/AIDS when Human Herpes Virus 8 (HHV-8) infection is also prevalent. The low incidence of Kaposi sarcoma observed in South Africa in the pre-AIDS era,[31,32] despite the moderate prevalence of HHV-8 observed in opportunistic sero-survey data,[33–35] would be consistent with the contention that other cofactors play a role in the development of Kaposi sarcoma.[36] While increases in the incidence of Kaposi sarcoma have been reported by the national cancer register since the start of the HIV/AIDS epidemic,[1] the national rates remain comparatively low (Table 2).

Childhood cases (<15 years) accounted for 2.9% (73 cases) of the total cancers during the 1998–2002 period. There has been a considerable increase on cases reported when compared with the previous report[15] and probably indicates an improvement in registration as a consequence of the extension of networks included in the Western Cape Paediatric Oncology Registry. However, the rates of childhood cancer may be understated. Cancers with genetic predisposition (retinoblastoma and nephroblastoma) when combined, constituted 35.6% of the childhood cancers reported.

Conclusion

Establishing and running a population-based cancer registry in a rural setting with limited resources is challenging. Not

only does it require a reliable system to capture and process all the cancer cases that occur in the area, but is highly dependent on the clinical capacity and health services infrastructure in the area, as well as individual health seeking behaviour of the community. Furthermore, it is taxed by work-related population migration, as well as migration directly related to access to health services. Special efforts have been made to develop collaborative networks with the health facilities inside the registration area and in referral centres to maximize the completeness of registration and ensure the quality of data. Nevertheless, incidence rates for some cancers may be underestimated. In particular lymphomas and haematological cancers might be under-counted as a result of limited diagnostic and treatment services.

The cancer registry in the former Transkei region of the Eastern Cape Province remains the only cancer registry established in a rural setting in Africa. It has been possible to maintain such a register because South Africa has a national public health infrastructure with hospital services reaching all districts. Despite some uncertainty in the rates, the registry contributes comparative information that can assist in tracking the diversity of cancer patterns. It also highlights the occurrence of cancer in rural areas and the need to implement cost-effective cancer control programmes as well as appropriate health services in under-resourced areas. This study will form a baseline for the newly extended surveillance area.

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II

Trends in cancer incidence in rural Eastern Cape Province, South Africa, 1998–2012.

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Trends in cancer incidence in rural Eastern Cape Province; South Africa, 1998–2012

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There are few cancer trend data reported in sub-Saharan Africa notably due to the scarcity of population-based cancer registries (PBCRs). The Eastern Cape Province PBCR is amongst the few registries in sub-Saharan Africa that reports data for a rural population. Trends in cancer incidence are reported for the period 1998–2012. Registered cases, age-standardized rates (ASRs) and standardized rate ratios are presented for the most common cancers in both males and females in three periods (1998–2002, 2003–2007 and 2008–2012). In males, the most commonly diagnosed cancer during the 15 year period was cancer of the oesophagus; incidence rates showed a significant decline over the 15 year period, entirely due to a 30% decrease between 2003–2007 and 2008–2012, to an ASR of 23.2 per 100,000 population. This was followed by prostate cancer, the incidence of which was more than doubled to a level of 9.9/100,000. In women, cancer of the cervix uteri has become the most common malignancy, with a significant increase in incidence during the period to 29.0/100,000. Oesophageal cancer is second in frequency, with (as in males) a significant decline in the final 10 years to an incidence of 14.5/100,000 in 2008–2012. The incidence of breast cancer increased by 61%, although the absolute rate remains low (12.2/100,000). The incidence rates of colorectal cancer are low, and the increases in incidence, although relatively large (35% in men, 63% in women) were not statistically significant. Kaposi sarcoma showed a dramatic increase in incidence in both sexes (3.5-fold in men, 11-fold in women) although the incidence remains relatively low by southern African standards. Cancer prevention and control activities in the area need to be informed by these data and strengthened.

There are very few data on trends in cancer incidence in sub-Saharan Africa, because of the absence of accurate and valid systems of cancer surveillance (notably cancer registries, given the absence of comprehensive vital registration). In South Africa, mortality statistics, based on registrations of deaths by cause, are routinely published, although in the earlier years at least, they were evaluated as "low quality" because of incomplete coverage and/or a high proportion of ill-defined causes of death.[1] The National Cancer Registry of South Africa records pathology diagnoses of cancer, from laboratories around the country, and since 1990 has issued several reports, although the most recent was for 2004 (http://www.afcrn.org/membership/members/87-ncrsa). Currently, the only population-based cancer registry is in the former Transkei region of the Eastern Cape Province of South Africa, founded in the early 1980s. Originally focused on esophageal cancer, in 1998 the registry expanded its scope (to collect data on all cancers), and geographic coverage. The results for the population of eight magisterial areas (Butterworth, Centane (Kentani), Idutywa, Nqamakwe, Willowvale, Bizana, Flagstaff and Lusikisiki) have been published previously.[2,3] Here we compare the incidence rates in three five-year time periods (1998–2002, 2003–2007 and 2008–2012).

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Material and Methods

The methods used to register cancer cases in this rural population have been described previously.[2] The registry collects data on cancer cases resident in the eight magisterial areas from all hospitals in which they are likely to have been diagnosed (and treated), both within the surveillance area as well as the major public sector centers to the north and south of it, to which patients from the area would be expected to be referred. In total, 15 hospitals (eight district, six referral) and a regional laboratory under the National Health Laboratory Services (NHLS) are used in case finding. Data are manually abstracted from the records and include demographic variables, tumor characteristics including the site, type and behavior. Cancer diagnoses are coded for topography and morphology according to the International Classification of

Short Report

What's new?

In South Africa, there is a single population-based cancer registry (PBCR), the Eastern Cape Province PBCR. Since 1998, This PBCR has captured data on multiple cancers for a rural population. The present report describes cancer incidence rates from PBCR data for the period 1998–2012. Among the most commonly diagnosed cancers in men for that period were esophageal and prostate cancers. For women, cervical and esophageal cancers were common. The analysis offers fresh perspective on cancer in a rural African population and highlights a need for ongoing cancer surveillance in the region.

Diseases for Oncology (ICD-O)[4] and entered into a database managed with the CanReg software a computer program designed by the Unit of Descriptive Epidemiology of the International Agency for Research on Cancer.

Population

The 1996, 2001 and 2011 censuses provide age-sex specific counts of the population of each of the eight magisterial areas.[5] The annual rates of change (by age, sex and area) in between these years were used to prepare annual estimates for 1998–2000, 2002–2010, and (based on annual change 2001–2011) for 2012. The average annual population at risk for the whole population of the eight magisterial areas was calculated for the three five year periods 1998–2002, 2003–2007 and 2008–2012. The distribution by age and sex at the censuses is shown in Figure 1.

Data analysis

Only malignant cases are included in the analysis; cases from outside the registration area have been excluded. The number of cases and annual incidence rates for the six most common cancers, and all cancers, of males, and the seven most common (plus "all cancers") in females were obtained by 5-year age group and sex. Age standardized rates (ASRs) were calculated according to the direct method, using the World Standard Population. The standard errors of the ASRs, and of the ratio of the ASRs in pairs of time periods (the standardized rate ratio (SRR)), were calculated.[6]

Results

Table 1 (upper half) shows the number of cases registered in the three periods, and the age standardized incidence rates for the six cancers (and "all cancers") in males, and seven (plus "all cancers") in females. The ASRs in the three time periods, with their 95% confidence intervals, are shown graphically in Figure 2. The standardized rate ratios comparing the ASRs in Period 2 (2003–2007) with those in Period 1 (1998–2002), Period 3 (2008–2012) *vs.* Period 2 and Period 3 *vs.* Period 1, with their 95% confidence intervals, are shown in the lower half of Table 1.

The most commonly diagnosed cancers during the 15 year period was cancer of the oesophagus (1,280 cases in males, 1,424 cases in females); there was a significant decline in the ASR between Period 2 and Period 3 (but not earlier), so that, over the whole period, there was a significant 30% decrease in incidence in both sexes. Cancer of the cervix uteri is the most common malignancy of women (1,787 cases); there has been a marked increase in incidence with the ASR in the third five-year period 31% higher than in the first (95% confidence interval of the SRR 1.17–1.48). The change in the incidence of breast cancer between Periods 1 and 3 was even greater (SRR 1.61 (95% CI 1.33–1.95), entirely due to the big rise between the second two periods (2003/7–2008/12).

Cancer of the prostate more than doubled in incidence (SRR 2.43, 95% CI 1.85–3.20), but the most dramatic increases were for Kaposi sarcoma in both sexes (SRR in males 3.47 and in females 10.70). Cancers of the colon/rectum showed quite large increases over the 15 year period in both sexes (SRR 1.35 and 1.63 in males and females, respectively), although non-significant because of the rather small numbers of cases, while liver cancer increased in females (SRR 1.66 95% CI 0.99–2.80) but not in males. There were no significant changes in the incidence of cancer of the lung.

Discussion

The area covered by the registry is almost entirely rural, and more than 97% of the population of the area are Xhosa speaking black Africans. The main economic activity is subsistence farming, but much of the population relies on remittances from migrant laborers in other parts of South Africa. This is reflected in the population structure (Fig. 1) which shows the relative excess of children and older persons, particularly women, and a deficit of working age adults, especially males. Labor migration is historically significant in South Africa. Such a migratory pattern may result in a lower cancer incidence being experienced in the area as it is possible that people from this area that develop a cancer while working in an urban area do not return to their rural home. On the other hand, some patients diagnosed elsewhere might return home to die and would inflate the incidence rate if they had not been counted in area at the time of the census. However, this is likely to have a limited effect as only those patients who receive treatment at the collaborating health facilities are included in the register.

The registry was established to aid studies of oesophageal cancers, and the incidence rates of this malignancy in the rural population of the Eastern Cape Province are indeed high—the highest in Africa.[7] Many studies have been conducted by scientists in South Africa to understand the aetiology of oesophageal cancer in this population. These include studies on genes and environment,[8–10] diet, cultural behavior and food contaminants.[11–14] However, the cause of the high incidence remains elusive, but, whatever is responsible, it is

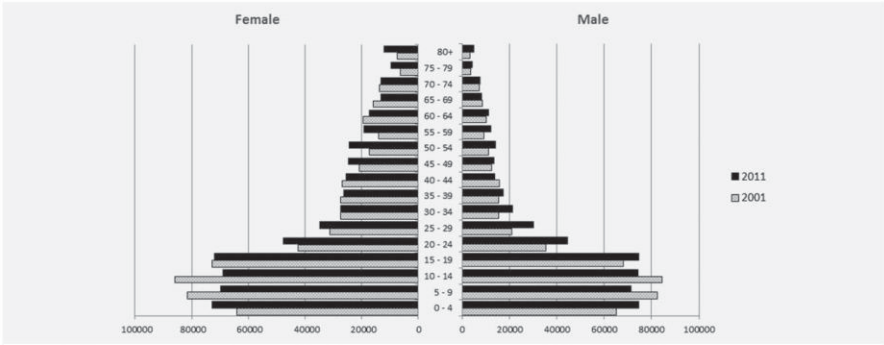

Figure 1. Population pyramids, 2001 and 2010. Eight magisterial areas, Eastern Cape Province, South Africa.

Table 1. Incident cases, annual age-standardised rates (ASR) per 100,000 population and standardised rate ratios (SRR) by site and sex for 1998–2002 (period 1), 2003–2007 (period 2) and 2008–2012 (period 3)

	MALE									FEMALE								
	1. 1998-2002			2. 2003-2007			3. 2008-2012			1. 1998-2002			2. 2003-2007			3. 2008-2012		
	Cases			Cases			Cases			Cases			Cases			Cases		
	No.	(%)	ASR (per 10^5)	No.	(%)	ASR (per 10^5)	No.	(%)	ASR (per 10^5)	No.	(%)	ASR (per 10^5)	No.	(%)	ASR (per 10^5)	No.	(%)	ASR (per 10^5)
Oesophagus	444	43%	32.4	475	43%	32.8	361	30%	23.2	481	32%	20.6	532	31%	20.4	411	20%	14.5
Large bowel	27	2.6%	1.9	34	3.1%	2.4	37	3.1%	2.6	20	1.4%	0.9	29	1.7%	1.2	43	2.1%	1.5
Liver	62	6.1%	4.4	38	3.4%	2.8	65	5.4%	4.2	21	1.4%	0.9	28	1.7%	1.2	42	2.0%	1.6
Lung	74	7.2%	5.8	68	6.1%	4.9	65	5.4%	4.2	18	1.2%	0.8	20	1.2%	0.9	28	1.3%	1.0
Kaposi	22	2.2%	1.7	42	3.8%	3.2	85	7.0%	5.8	7	0.5%	0.3	31	1.8%	1.4	79	3.8%	3.5
Breast										162	11%	7.6	175	10%	7.5	299	14%	12.2
Cervix										491	33%	22.1	577	34%	24.6	719	35%	29.0
Prostate	69	6.8%	4.1	106	9.5%	6.3	225	19%	9.9									
All sites	1,022	100%	72.5	1,114	100%	75.6	1,206	100%	76.6	1,481	100%	65.2	1,695	100%	69.3	2,080	100%	80.9

	Period 2 v Period 1		Period 3 v Period 2		**Period 3 v Period 1**		Period 2 v Period 1		Period 3 v Period 2		**Period 3 v Period 1**	
	SRR	95% c.i.	SRR	95% c.i.	**SRR**	**95% c.i.**	SRR	95% c.i.	SRR	95% c.i.	**SRR**	**95% c.i.**
Oesophagus	1.01	(0.89-1.16)	0.71	(0.61-0.81)	**0.72**	**(0.62-0.83)**	0.99	(0.88-1.13)	0.71	(0.62-0.81)	**0.71**	**(0.62-0.81)**
Large bowel	1.26	(0.75-2.11)	1.07	(0.67-1.72)	**1.35**	**(0.81-2.24)**	1.29	(0.73-2.29)	1.26	(0.78-2.04)	**1.63**	**(0.96-2.75)**
Liver	0.63	(0.42-0.95)	1.49	(1.00-2.23)	**0.94**	**(0.66-1.35)**	1.27	(0.72-2.26)	1.31	(0.80-2.12)	**1.66**	**(0.99-2.80)**
Lung	0.85	(0.60-1.18)	0.85	(0.60-1.21)	**0.72**	**(0.51-1.02)**	1.03	(0.54-1.98)	1.20	(0.66-2.15)	**1.24**	**(0.68-2.26)**
Kaposi	1.93	(1.15-3.23)	1.80	(1.25-2.59)	**3.47**	**(2.24-5.36)**	4.11	(1.94-8.69)	2.60	(1.74-3.90)	**10.70**	**(5.83-19.65)**
Breast							0.99	(0.79-1.23)	1.63	(1.35-1.97)	**1.61**	**(1.33-1.95)**
Cervix							1.12	(0.99-1.26)	1.18	(1.05-1.32)	**1.31**	**(1.17-1.48)**
Prostate	1.56	(1.14-2.12)	1.56	(1.23-1.99)	**2.43**	**(1.85-3.20)**						
All sites	1.04	(0.95-1.14)	1.01	(0.93-1.10)	**1.06**	**(0.97-1.15)**	1.06	(0.99-1.14)	1.17	(1.09-1.25)	**1.24**	**(1.16-1.33)**

possible that there has been some recent change in exposure levels.

The biggest change in cancer incidence over the 15 year period is the marked increase in Kaposi sarcoma. However, despite the high prevalence of HIV in the region,[15] incidence rates are surprisingly low when compared to sub-Saharan Africa and southern Africa rates. In both Uganda (Kampala) and Zimbabwe (Harare), the incidence of Kaposi sarcoma has declined in the last decade, coinciding with a decline in HIV prevalence and increasing availability of anti-retroviral therapy.[16,17] However, in South Africa, population-based sero-surveys and sentinel surveillance of pregnant women suggest that the HIV prevalence increased from 1990 to reach a plateau in 2005, and has remained constant since then.[15] A record review in oncology clinics in KwaZulu-Natal showed a steep increase in the diagnosis of Kaposi sarcoma in the period 1983–2006.[18] It is unlikely that many patients with HIV-AIDS in the registry areas had ready access to ART in this time period.

In South Africa, the incidence rates of prostate cancer for white men have been much higher than the rates for black men.[19] The lower rates in black men are also associated with poor access to diagnostic and screening facilities. Rates in the Eastern Cape Province, although increasing, remain low (ASR 9.9 per 100,000 in 2008–2012). The increase in incidence is

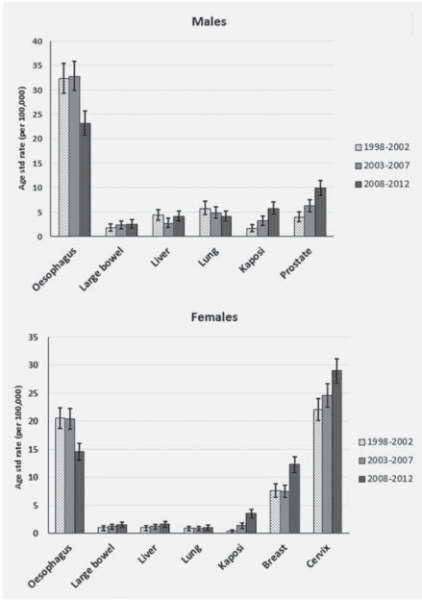

Figure 2. Age standardized incidence rates (per 100,000 population) with 95% confidence intervals, for three time periods (1998–2002; 2003–2007; 2008–2012) in males (upper half) and females (lower half).

similar to the observations in Uganda[16] and Zimbabwe.[17] Large increases in incidence of prostate cancer in the last 20 years have been observed in high income countries, where much can be ascribed to screening with PSA. This is certainly not a factor in the increase in the Eastern Cape Province, where increased awareness, a greater readiness to perform prostatectomy for urinary symptoms in elderly men and histological examination of operative biopsies may partly explain the observed changes.

The incidence of cervix cancer is high, but the trend in the incidence is at variance with that derived by modeling of South African data, which predicts declining rates.[20] However, with almost no access to screening programs, and increasing rates of other HIV-related cancers, an increase, similar to that observed in Kampala and Harare,[16,17] is not surprising.

While cervical cancer rates are extremely high, the incidence of breast cancer is very low (ASR of 12.2 per 100,000 in 2008–2012), even by African standards.[7] Certain factors known to be important in the epidemiology of breast cancer that are unique to black women include late menarche, relatively early age at birth of the first baby, high parity and prolonged lactation.[21] Presumably, the increase in incidence reflects changes in fertility patterns in this rural population, as well as other lifestyle features such as increasing obesity. Fertility in South Africa has declined rapidly, especially since the late 1960s.[22] The pace of this decline is very rapid in comparison with sub-Saharan Africa as a whole, and can be observed even in poorer rural populations.[23] The prevalence of overweight and obesity, already high among South African females, is also increasing.[24]

Conclusions

There are few data on temporal trends of cancer in Africa, and these are the only ones to document changes in incidence in a rural population. Current wisdom is that, with westernization of lifestyles (tobacco use, dietary habits, fertility, body weight, physical activity), there will be an increase in the incidence of cancers common in populations of European origin (breast, large bowel, lung). While, to some extent, such changes can be seen in this rural population of Eastern Cape Province, there has been no corresponding decrease in cancers associated with poverty (liver, cervix uteri), and, so far, no diminution in Kaposi sarcoma, which is essentially the result of infection with HIV/AIDS.

To date, little has been done by way of cancer prevention and control. While the etiology of oesophageal cancer remains obscure, prevention is problematic, but the high rates of cervix cancer demand a greater commitment to expanding cervical cancer screening and HPV vaccination in girls to prevent future cases.

Finally, these data show the importance of ongoing monitoring of cancer incidence, and the role of population-based cancer registries, without which no rational approach to cancer control is possible.

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III

Increasing cervical cancer incidence in rural Eastern Cape Province of South Africa from 1998 to 2012

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original reports abstract

Increasing Cervical Cancer Incidence in Rural Eastern Cape Province of South Africa From 1998 to 2012: A Population-Based Cancer Registry Study

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PURPOSE In this study, we aimed to investigate trends in the age-standardized and age-specific incidence rates in two distinct regions (the northern and southern areas) of South Africa covered by a population-based cancer registry. In addition, trends in coverage of the cervical cancer screening program were assessed using routine health service data.

METHODS Occurrences (topography C53.0-C53.9) for the period 1998-2012 were extracted from a cancer registry database from which basic descriptive statistics and frequencies were analyzed for all variables using CanReg4. Trends over time were estimated using a direct standardization method and world standard population as a reference. Screening coverage annualized figures for women age ≥ 30 years by sub–health district were extracted from the District Health Information System.

RESULTS In the northern area, annual age-standardized incidence rates per 100,000 women increased from 24.0 (95% CI, 21.1 to 27.0) in 1998-2002 to 39.0 (95% CI, 35.6 to 42.5) in 2008-2012, with a screening coverage rate of 15% by 2012. In contrast, no increase was observed in incidence in the southern area, with rates of 20.0 (95% CI, 18.5 to 21.4) in 1998-2002 and 18.8 (95% CI, 16.2 to 21.4) in 2008-2012, and the southern area had a higher screening coverage of 41% in 2012. Overall, the percentage distribution of stage at diagnosis showed that 28.5% of occurrences were diagnosed at disease stages I and II and 35%, at III and IV; 36% had with missing stage information (2003-2012). In 77% of occurrences, a histologically verified diagnosis was made, compared with only 12.3% by cytology.

CONCLUSION This study has demonstrated an almost two-fold increase in the incidence rate in the northern area but little change in the southern area of the cancer registry.

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INTRODUCTION

Globally, cervical cancer accounts for 6.6% of all cancers reported in women and is ranked as the fourth highest cause of both incidence and mortality.[1] There were an estimated 570,000 new occurrences and 311,000 deaths from cervical cancer worldwide in 2018. Of this global burden, cervical cancer accounts for 90% of deaths in women living in low- and middle-income countries (LMICs), with the highest burden borne by countries in sub-Saharan Africa. This contrasts with the much lower incidence rates of 10.4 per 100,000 women in developed countries. During the past few decades, cervical cancer incidence and mortality rates have been in decline in many populations worldwide. Aside from screening (where available), these declines have been ascribed to factors linked to either increasing average socioeconomic levels or a diminishing risk of persistent infection with high-risk human papillomavirus (HPV) or other sexually transmitted diseases. Cervical cancer treatment takes approximately 18% of a health facility's budget, yet it is preventable and can be diagnosed early through screening using various methods—with the Papanicolau (Pap) test as the gold standard.[2]

Cervical cancer is the second most common cancer among women in South Africa after breast cancer.[3] The National Cancer Registry reported age-standardized incidence rates (ASRs) of 26.2 and 29.1 per 100,000 for black African women in 2008 and 2012, respectively. The population-based Eastern Cape Cancer Registry (ECCR) that records incident cancer occurrences among a population living in a defined rural area also reported an increase in cervical cancer ASRs from 22.0 to 29.4 per 100,000 women during the same period.[4]

South Africa adopted a cytology-based screening program for cervical cancer in 1999 as part of its National Cancer Control Policy.[5] Women attending the

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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public-sector services would be entitled to three free Pap smears per lifetime starting at the age of 30 years or older, with a 10-year interval between each smear unless the smears reveal dysplastic or atypical cellular changes. The goal of this screening program was to screen 70% of the target population within 10 years of implementation. However, small-scale screening evaluation studies identified problems with the implementation of the program. These problems were associated with level of recipients' knowledge about screening, health system implementation challenges, and limited population coverage.[6] Findings of other studies conducted in the Western Cape,[7,8] the Free State,[8] and KwaZulu-Natal[9] also revealed fragmented services with little or no follow-up for women with positive smears. These studies also highlighted the unequal distribution of resources, which was worse in rural clinics.[9]

It has been demonstrated that women with HIV/AIDS have significantly higher rates of cervical cancer than the general population.[10] However, there have been mixed findings about the effect of antiretroviral therapy (ART)/highly active ART. Unlike other AIDS-defining cancers, the incidence of cervical cancer does not seem to have diminished after the advent of ART.[11] Conversely, a global systematic review showed that women with HIV who receive ART have a lower prevalence of high-risk HPV and experience a reduction in the incidence of invasive cervical cancer.[12] Additional studies with larger sample sizes and cohort designs were encouraged.[11]

It is unclear whether the observed increase in cervical cancer incidence in this study population is related to increased availability of free screening or other factors. This study was designed to investigate trends in the age-standardized and age-specific incidence rates in two distinct regions (the northern and southern areas) covered by the ECCR. In addition, trends in coverage of the cervical cancer screening program were assessed using routine health service data.

METHODS

Study Population

The ECCR collects data for the population living in two distinct rural areas in the former Transkei region of the Eastern Cape Province of South Africa, originally selected for monitoring esophageal cancer in four magisterial areas (Fig 1). In 1998, the surveillance scope was expanded to

FIG 1. Map of South Africa showing cancer registration area in the Eastern Cape Province.

include eight magisterial areas, of which three (Bizana, Flagstaff, and Lusikisiki) form the northern part in the Alfred Nzo Health District and five (Butterworth, Centane/Kentani, Idutywa, Nqamakwe, and Willowvale) form the southern part in the Amathole Health District.

The ECCR covers a population of just more than 1 million; 54% are women, and 46% are men, according to the population census (2011).[13] ECCR data account for 16% of the population residing in the Eastern Cape Province, and the age-sex composition in the population pyramid is typical of a rural setting (Fig 2). South Africa is an upper-middle income country but experiences high unemployment, poor economic growth, and very high wealth inequalities. The study population included communities with higher-than-average proportions living below the poverty line[14] and the highest rates of HIV,[15] and AIDS accounted for 31.5% of deaths experienced in the province.[16]

Data Collection Method

The ECCR is one of two rural population-based cancer registries in Africa with important features for maintaining data quality, as described previously.[4,17] Both active and passive case-finding methods are used to collect data. Medical records, including pathology reports, are viewed, and cancer information is abstracted manually for each patient diagnosed using a structured data collection tool. Identified duplicates are managed accurately and deleted when the patient information is consolidated. A customized cancer registry data management program, CanReg4 (International Agency for Research on Cancer, Lyon, France) is used.[18]

Statistical Analysis

Basic descriptive statistics and frequencies were analyzed for all variables using CanReg4. Analysis of the collected data provided occurrences reported by age, year, and magisterial areas. The average annual population at risk was calculated for the three 5-year periods (1998-2002, 2003-2007, and 2008-2012). The 1996, 2001, and 2011 censuses[13] provided age-specific counts of the population. The annual rates of change (by age, sex, and magisterial area) between these years were used to prepare annual and 5-year period estimates. A direct method, as described by Boyle and Parkin,[19] was adopted to calculate ASRs per 100,000 person-years. The world standard population was used as the reference population.[20] Weighted standard errors were calculated to provide 95% CIs for the ASRs.

Topography C53.0-C53.9 according to International Classification of Diseases—Oncology (ICD-O)[21] for the period 1998-2012 were extracted from the ECCR database. The annual cervical cancer incidence trends were calculated for the years 1998-2012, a 15-year period encompassing the initiation of the national cervical cancer free cytology screening program in South Africa. Information was checked on the age and stage distribution of incident occurrences (stages I and II *v* III and IV) to assess the proportion of occurrences diagnosed early in the progression of the disease. The proportion of occurrences with pathologically verified diagnoses was calculated to check the proportion of cytology-identified versus histology-verified occurrences in particular. Subanalyses were conducted for the distinct northern and southern areas of the region covered by the registry.

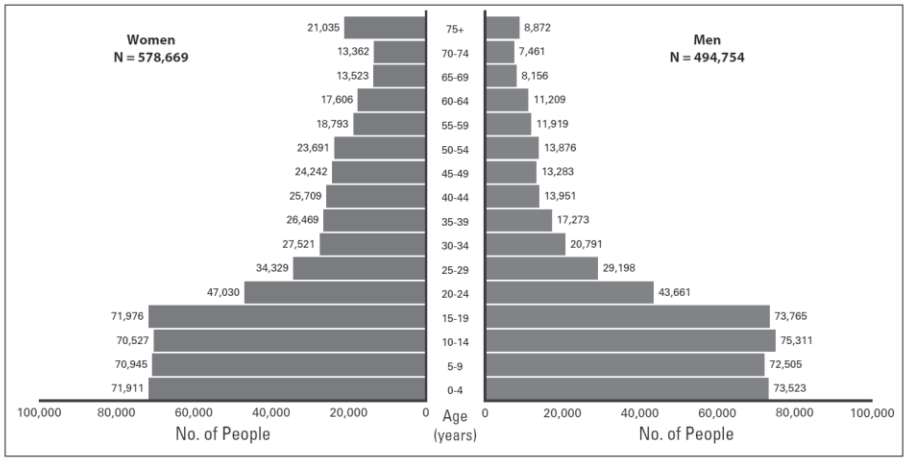

FIG 2. Estimated average annual population of eight magisterial areas for the period of 2008-2012.

Screening Coverage Data and Analysis

The District Health Information System (DHIS) collects monthly facility-based data from all public-sector clinics and hospitals across the country. From 2007 on, a data element was added on the basis of the number of women older than age 30 years who had a Pap test in the past month. An annualized indicator for screening coverage calculated using the DHIS population estimate is reported. DHIS data were obtained from the National Department of Health, and annualized figures of screening coverage for women age ≥ 30 years were extracted for the Mbashe, Mnquma, and Qaukeni Health subdistricts. With small boundary variations, the eight magisterial areas can be mapped directly onto the three health subdistricts. The coverage indicator in the DHIS has been calculated by taking the number of women age ≥ 30 years who were screened divided by the number of women in the target population, divided by 10 to account for a cervical cytology–based screening policy that aimed to screen once every 10 years.

Approved ethics. The South African Medical Research Council Ethics Committee approved the study proposal; Protocol ID No. EC014-10/2014 was assigned on February 23, 2015. The Eastern Cape Health Research Committee approval No. EC RP52-33 was designated on May 12, 2015.

RESULTS

A total of 1,808 new occurrences were reported; 63% were from the northern area of the registry, and 37% were from the southern area. Table 1 lists the basis of diagnosis and the stage of the cervical cancer by area and period. Overall, histologically verified diagnoses ranged between 64.7% and 73.6%, whereas cytologically verified diagnoses ranged between 7.9% and 12.5%; clinically diagnosed occurrences ranged between 27.4% and 14.0%. Histologic verification by areas ranged between 65.8% and 71.3% in the northern area and between 63.6% and 77.7% in the southern area; respective regional cytologic diagnoses ranged between 5.8% and 13.6% and 10.2% and 10.4%. Occurrences without additional confirmatory tests in the northern and southern areas ranged between 28.4% and 15.1% and between 26.3% and 11.9%, respectively.

Information about the stage of disease at diagnosis was collected by the ECCR from 2003 onward, and the results for the two periods (2003-2007 and 2008-2012) are presented in Table 1. During 2003-2007, 29.4% of the occurrences had missing stage information, and this increased to almost half (42.4%) in 2008-2012. The proportion with missing stage information differed; in the northern area, it ranged between 33.0% and 46.3%, whereas it ranged between 23.2% and 34.2% in the southern area. Stage III was the most common stage at diagnosis, and its rate increased from 23.7% in 2003-2007% to 25.7% in 2008-2012.

TABLE 1. Basis of Diagnosis and Stage at Diagnosis of Cervical Cancer Occurences by Area and Period, Eastern Cape Cancer Registry

Variable by Area	% by Time Period		
	1998-2002	2003-2007	2008-2012
Northern area			
No. of women	265	361	512
Basis of diagnosis			
Histology	65.8	59.6	71.3
Cytology	5.8	5.8	13.6
Clinical[a]	28.4	34.5	15.1
State at diagnosis			
I and II		30.3	20.3
III and IV		36.8	33.3
Unknown		33.0	46.3
Southern area			
No. of women	228	216	226
Basis of diagnosis			
Histology	63.6	66.1	77.7
Cytology	10.2	9.2	10.4
Clinical[a]	26.3	24.8	11.9
Stage at diagnosis			
I and II		38.6	31.1
III and IV		38.2	34.7
Unknown		23.2	34.2
Eastern Cape Registry			
No. of women	493	577	738
Basis of diagnosis			
Histology	64.7	62.0	73.6
Cytology	7.9	7.1	12.5
Clinical[a]	27.4	30.8	14.0
Stage at diagnosis			
I and II		33.3	23.8
III and IV		37.3	33.8
Unknown		29.4	42.4

[a]Without laboratory confirmation.

ASRs per 100,000 of women are reported for three periods by area in Figure 3. Overall ASRs per 100,000 women were 22.0 (95% CI, 20.0 to 24.0) in 1998-2002, 24.4 (95% CI, 22.4 to 26.4) in 2003-2007, and 29.2 (95% CI, 27.3 to 31.6) in 2008-2012. Although the ASR in the entire region showed a progressive increase, there was a slight decrease in the southern area during this period. ASRs per 100,000 women were 20.0 (95% CI, 18.5 to 21.4) in 1998-2002, 19.1 (95% CI, 16.5 to 21.7) in 2003-2007, and 18.8 (95% CI, 16.2 to 23.4) in 2008-2012. These differences were not statically significant. In contrast, the ASRs in the northern area increased significantly from 24.0 (95% CI, 21.1 to 27.0) in 1998-2002 to 29.7 (95% CI, 26.6 to 32.8) in 2003-2007 and 39.0 (95% CI, 35.6 to 42.5) in 2008-2012.

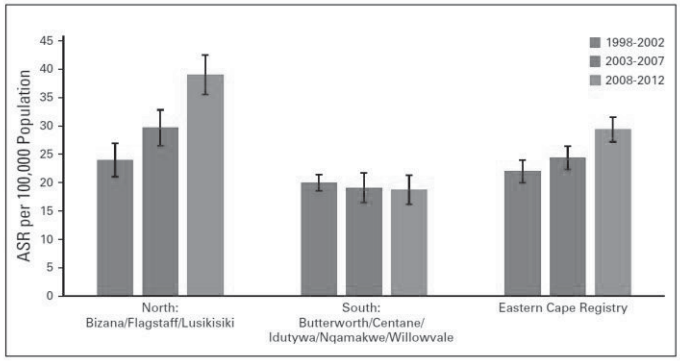

FIG 3. Age-standardized annual incidence rates for cervical cancer over time periods by area, Eastern Cape Cancer Registry. ASR, age-standardized rate.

The ASRs are shown for the three periods in Figures 4A (northern) and 4B (southern). Incidence increased steadily by age, with a decrease at ≥ 70 years. In the northern area (Fig 4A), a distinct increase was observed during the third period (2008-2012); the increase occurred across all ages but was more marked in the 50-59 years and 60-69 years age groups. In the southern area (Fig 4 B), little difference was observed across the three periods.

Screening Coverage Proportions

The cervical screening coverage results for women age ≥ 30 years are listed by health subdistrict and year in Table 2. Inclusion of these data in the routine information systems started in 2007 but had particularly low coverage in the northern area (2.2% in 2007 and 4.3% in 2008). An increase was observed from 2009 to 2012 to a maximum of only 14.8% in 2012. The southern area reported slightly better coverage of the screening program, with an average of 7.7% in 2007, an increase to 41.0% in 2012, and anomalously high coverage of 69.0% reported for Mbashe in 2010. Furthermore, this subdistrict had almost twice the screening percentage of the Mnquma subdistrict (52.3% *v* 29.7%) in 2012.

DISCUSSION

Compared with the global average cervical cancer incidence rates of 6.9 per 100,000 women in 2012,[22] the rates of 18.8 (95% CI, 16.2 to 21.4) and 39.0 (95% CI, 35.6 to 42.5) per 100,000 women reported in the study population (Fig 3) are unacceptably high. Incidence rates increased significantly over time in the northern area, contributing to the previously reported overall increase.[4] Several factors could be associated with the increasing trends, including increased population-based screening and the high prevalence of HIV. Conversely, the incidence rates in the southern area showed a slight decrease, which was not statistically significant.

The proportion of patients with cytologically confirmed cervical cancer increased in the northern area from 5.8% to

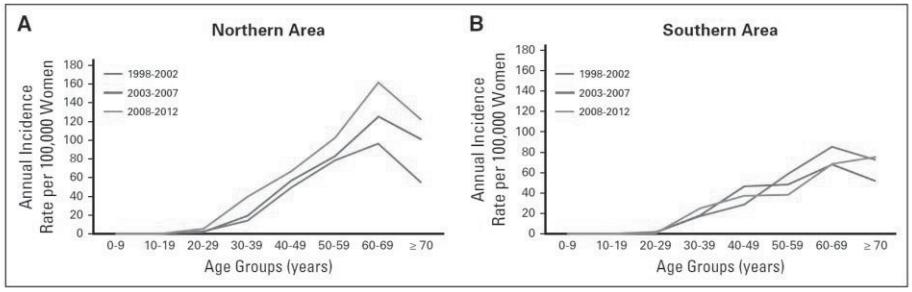

FIG 4. Age-specific annual incidence rates for cervical cancer over time periods by area, Eastern Cape Cancer Registry.

TABLE 2. Percentage of Cervical Screening Coverage Among Women 30 Years and Older by Area, 2007-2012

	Northern Area	Southern Area	
Year	Qaukeni Subdistrict (magisterial areas: Bizana, Fagstaff and Lusikisiki)	Mbhashe Subdistrict (magisterial areas: Idutywa and Willowvale)	Mnquma Subdistrict (magisterial areas: Butterworth, Centane and Nqamakwe)
2007	2.2	7.9	7.5
2008	4.3	34.4	15.3
2009	10.6	43.8	16.4
2010	11.8	69.0	25.6
2011	14.0	46.6	30.0
2012	14.8	52.6	29.7

13.6% in the final period, whereas the proportion in the southern area remained stable at approximately 10% across the whole study period (2007-2012). Data from the DHIS showed that screening coverage increased in both study areas, albeit to less than optimal levels (Table 2). It appears that the southern area experienced better coverage, reaching levels of 41% in 2012, compared with the northern area, which reached only 15%. Given the contrasting trends between screening and incidence, it appears unlikely that the increase in incidence observed in the northern area could be ascribed to increased access to the screening program.

The high cervical cancer incidence experienced in this population might be due to the high burden of HIV infection, which concurs with studies that were conducted in South Africa and Rwanda.[23,24] Both studies observed a strong association between HIV and cervical cancer. Stein et al[24] observed an increased risk of cervical cancer associated with HIV (odds ratio, 1.6; 95% CI, 1.3 to 2.0) in a case-control study conducted in South Africa, whereas Mpunga et al[23] observed an even stronger association in Rwanda (odds ratio, 5.9; 95% CI, 3.8 to 9.2). Despite consideration of cervical cancer as an AIDS-defining cancer, conflicting trends have been observed. Early reports found no association between HIV and the incidence of cervical cancer.[25] Late-stage HIV infection was associated with Pap test abnormalities at a younger age[26], which also was observed in a study in South Africa.[27] Both Moodley[28] and the International Agency for Research on Cancer Working Group on the Evaluation of Carcinogenic Risks to Humans reported a reduction of invasive cervical cancer incidence in an area of high HIV prevalence and noted that cervical cancer was not an AIDS-defining condition in the African setting.[28, 29]

South Africa is in the throes of an HIV/AIDS pandemic that has affected both areas of the ECCR. In 2012, the prevalence of HIV among pregnant women was 30.0% in the OR Tambo Health District (incorporating the northern area) and was 31.5% in Amathole Health District (incorporating the southern area).[30] Since 2008, there has been a countrywide rollout of ART. Unfortunately, small-area data on the provision of ART are unavailable. However, health service data point toward the possibility of a quicker rollout in the northern area. The OR Tambo District reported that 86.2% of antenatal clients identified as HIV positive initiated ART compared with 61.9% in Amathole.[30] The increased incidence of cervical cancer observed in the northern area does not appear to be associated with the screening program (Table 2) but may be associated with high HIV infection coupled by a quicker rollout of ART.

The Strategic Plan for the Prevention and Control of Non-Communicable Diseases identified the need to screen women with HIV infection for cervical cancer and other sexually transmitted diseases at a younger age and more frequently.[31] Presentation of patients at late stages of the disease may indicate that the diagnosis was made by clinical signs and symptoms rather than by screening. The high incidence rates, together with a low proportion of cytologic confirmation, are indicative of a low reach of screening in this area. Other factors include poor infrastructure, which thus reduces the number of women effectively screened in South Africa[7-9] and Botswana.[9,32,33] Denny et al[34] viewed the coverage as more important than frequency of screening. In their randomized controlled trial, they used three screen-and-treat strategies that included screening by visual inspection with acetic acid. However, only women in an urban area participated in this study, which was not extended to rural women who have limited access to facilities.

Other factors that may have contributed to the high incidence of cervical cancer in this area are health inequity and low health-seeking behavior[35] with loss to follow-up after the initial screening test among women identified with abnormal cytology[9] and unequal distribution of resources.[6-9,36] In South Africa, better-equipped health facilities are those classified as secondary and tertiary hospitals in urban areas, and this location denies women living in rural areas an opportunity to receive medical attention in time and closer to home. Those in the study area with positive smears, for example, travel a distance of 100-600 km for better care and disease management at secondary and/or tertiary hospitals.

The study has several limitations. Many occurrences had missing staging information at diagnosis. This information is not part of mandatory variables collected by cancer registrars; rather, it is collected only when available during data abstraction. There were few occurrences with cytology as basis of diagnosis but a high percentage of histologically verified diagnoses, which was worrisome. Screening coverage proportions from the routine health data were based on aggregate data; the coverage proportions may be even lower than reported, and they do not distinguish the individuals who have been screened.

In conclusion, South Africa struggles with huge disparities in the health system capacity to address the growing

burden of cervical cancer, especially among rural populations. The scarcity of trained specialists coupled with the absence of resources for a robust primary care structure result in late diagnoses with poor survival for cervical cancer—a condition that often is an incurable but preventable disease. The increased cervical cancer incidence experienced by the population in this study may portend increases associated with the widespread provision of ART and low screening reach. The reviewed screening policy that included women with HIV and other sexually transmitted diseases show the South African government's commitment to addressing cervical cancer (Data Supplement). Unless innovative approaches to test for and treat this disease become available, serving a rural area will remain a major challenge. This study illustrates the contribution of a population-based cancer registry as an essential tool to inform cancer control efforts. Opportunities to strengthen and complement these data through data linkage with other information systems would facilitate additional research.

AFFILIATIONS

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Manuscript writing: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/go/site/misc/authors.html.
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