Primary cutaneous malignancies in the Northern Cape Province of South Africa:

a retrospective histopathological review

by

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KRGKAT002

Submitted to the University of Cape Town

in partial fulfillment of the requirement for the degree

Master of Medicine (MMed) in Dermatology

Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

14 April 2016

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Declaration

I, Dr Katherine York, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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Acknowledgements

I would like to express my sincere gratitude toward my three supervisors, Professor Nonhlanhla Khumalo, Professor Ncoza Dlova and Professor Anisa Mosam for the time and effort they have put into helping me with this endeavour. The infinite guidance, support and diligence they have shown is both remarkable and inspiring.

I also would like to express my appreciation towards Caradee Wright of the South African Medical Research Council and Patricia Kellet of the National Cancer registry for the information and advice they provided.

I am most grateful to Reshma Kassanjee of the UCT Department of Statistics for her assistance with the statistical analysis.

Abstract

Background: Excessive sun exposure and high human immunodeficiency virus prevalence increase skin cancer risk in South Africa.

Objective: To describe the nature and extent of skin cancers presenting in public and private health sectors of the Northern Cape Province.

Methods: A retrospective analysis of histologically-confirmed new primary cutaneous malignancies from 1/1/2008 to 31/12/2012 was conducted using public and private health sector databases. Types, quantity and distribution of common invasive malignancies by population group, age, gender, anatomical site and health sector were explored. One-year cumulative incidence was calculated and logistic regression models were used to analyse incidence and melanoma thickness trends.

Results: 4270 biopsies (14 cutaneous malignancies) were identified. Most common were Squamous Cell Carcinoma (SCC), Basal Cell Carcinoma (BCC), Kaposi Sarcoma (KS), Cutaneous Malignant Melanoma (CMM) and Basosquamous carcinoma. The odds of a White male developing SCC increased by 8% each year (OR: 1.08; CI: 1.01-1.15; p-value: 0.022) whilst the odds of a Black male developing SCC and KS decreased by 9% (OR: 0.91; CI: 0.84-0.99; p-value: 0.033) and 18% (OR: 0.82; CI: 0.70-0.97; p-value: 0.022) each year, respectively. SCC and CMM were diagnosed at more advanced stages within public versus private sectors. CMM is being detected earlier, as indicated by low stage depth increasing by 72% annually (OR: 1.72; 95% CI: 1.04-3.01; p-value: 0.042).

Conclusion: Results suggest that reported skin cancer patterns are changing. There is a need for further research and equitable appropriation of financial resources and effort toward developing primary skin cancer prevention initiatives in South Africa.

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Abbreviations

AIDS: acquired immune deficiency syndrome

ALM: acral lentiginous melanoma

ART: antiretroviral therapy

BCC: basal cell carcinoma

BSC: basosquamous carcinoma

CDC: Centre for disease control and prevention

CMM: cutaneous malignant melanoma

DMSA: Data Management and Statistical Analysis unit of South Africa

HHV8: human herpes virus 8

HIV: human immunodeficiency virus

HPV: human papilloma virus

KS: kaposi sarcoma

NC: Northern Cape

NCR: National Cancer Registry

NHLS: National Health Laboratory Service

NICE: National Institute for Clinical Excellence

NMSC: non-melanoma skin cancer

OCA: oculocutaneous albinism

OR: odds ratio

PUVA: psolaren and ultraviolet A radiation

SA: South Africa

SCC: squamous cell carcinoma

SCCI: squamous cell carcinoma insitu

SCFSA: Skin Cancer Foundation of South Africa

SNOMED: Systemised Nomenclature of Medicine

Stats SA: Statistics South Africa

SSA: Sub-Saharan Africa

UK: United Kingdom

USA: United States of America

UVR: ultraviolet radiation

Chapter 1: Introduction and literature review

1.1 Introduction

South Africa (SA) spans the latitude 22° S to 34° S and due to its location within the subtropics, most parts of the country have high levels of solar ultraviolet radiation (UVR).[1] This is particularly the case with the Northern Cape (NC) Province, which is the country's largest and most arid province, the vegetation consisting mainly of scrubland, with trees often limited to watercourses.[2] Despite its geographic size, the NC Province has the smallest population, with only 1.18 million individuals inhabiting it.[3] Its economy relies mainly on mining and agriculture, and 18.5% of the currently employed NC population work within the agricultural industry.[4] A total of 90% of Non melanoma skin cancer (NMSC) is attributed to personal exposure to UVR and thus South Africans are especially susceptible to skin cancer due to their year-round exposure to high ambient solar UVR.[5] Individuals working outdoors are at an even greater risk, as they will probably spend most daylight hours outside and thus have a 43% and 77% higher risk of developing basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) respectively.[6,7] The incidence of both NMSC and cutaneous malignant melanoma (CMM) is on the increase globally, with reporting systems being essential to monitor the number of cases and the trends over time.[8,9] However, due to limited private sector submissions to the South African National Cancer Registry (NCR), the last comprehensive data inclusive of all health sectors was published in 2004, making it difficult to establish whether skin cancer incidence in SA has followed the global trend.[10] This study therefore, aimed to collate and analyse public and private sector data for the NC province over a five-year period to provide insight into the local skin cancer burden and potentially give an indication of the skin cancer problem in SA at large. The literature review addresses issues relating to the pathogenesis of skin cancer, types of skin cancer, their origins and key characteristics, as well as risk factors for skin cancer development. It provides a global and local perspective on skin cancer incidence and reviews current initiatives to combat skin cancer in SA and the need for up-to-date skin cancer statistics.

1.2 Literature review

1.2.1 The pathogenesis of skin cancer

Carcinogenesis refers to the production of cancer, and it is a multistep process that occurs as a result of the accumulation of mutations in vital regulatory pathways which, after various stages of precancerous proliferation, result in the transition to the malignant phenotype.[11] Skin cancer is the uncontrolled growth of abnormal skin cells, its formation being based on constitutional and/or inherited factors often combined with environmental factors such as exposure to ultraviolet or ionizing radiation, various chemicals or oncogenic viruses.[12]

Exposure to ultraviolet light results in the formation of deoxyribonucleic acid (DNA) photoproducts and the generation of reactive oxygen species that cause DNA damage. UV-light damaged DNA is either repaired or if this cannot be done, the DNA damaged cells are removed by apoptosis. With excessive chronic exposure to UVR, repair pathways are overwhelmed, allowing photoproducts to persist, which interfere with DNA replication and result in mutations.[12] The starting point for the development of SCC is formation of mutations within the p53 tumour suppressor gene. The molecular basis for BCCs originate through UV light mediated mutations of the PTCH1 gene of the Hedgehog signalling pathway, this being vital to maintain cell growth and differentiation. Mutations in genes controlling cell proliferation and apoptosis result in clonal expansion, which results in various stages of precancerous proliferation ensuing and leads to the development of additional mutations, and ultimately transition to a malignant neoplasm.[12]

Oncogenic viruses can transform keratinocytes by activating cancer-promoting genes. The viral proteins may act directly as oncogenes that stimulate cells to multiply or they may initiate inflammatory responses and cause the regeneration of damaged cells that ultimately may lead to malignant transformation.[13] Ionising radiation can cause DNA damage directly itself or indirectly through free radical formation.[14] Chemical carcinogens may act as initiators, which directly cause mutations in DNA, or act as promoters that lead to proliferation of initiated cells.[15]

1.2.2 Types of skin cancer, their origins and key characteristics

Skin cancer is broadly divided into non-melanoma and melanoma skin cancers, the former referring to all other malignant tumours that arise in the cells of the skin other than melanocytes.[12] Melanocytes are melanin-forming cells located in the basal layer of the epidermis of the skin.[12] Melanoma skin cancer includes all types of CMMs, which are aggressive malignant tumors arising from melanocytes.[12]

1.2.2.1 Non-melanoma skin cancer

Eight broad groups of NMSC will be reviewed.

a. Basal cell carcinoma

BCC originates in the basal cell layer of the epidermis and is responsible for about 75% of NMSCs.[16] It typically develops on chronically sun-exposed areas of the skin, especially the head and neck.[16] It is slow growing and very rarely metastasizes, although if left untreated, it may spread to adjacent tissues and even bone. There are a number of BCC subtypes with different morphological characteristics namely nodular, superficial, morpheaform and fibroepithelial.[16]

b. Squamous cell carcinoma

SCC accounts for about 20% of NMSCs and originates from the more superficial layers of the epidermis with a tendency to be more aggressive than BCC.[17] It can invade adjacent tissues as well as spread to lymph nodes and distant sites. It usually appears on sun-exposed areas such as the face and backs of the hands, but also has a tendency to develop within areas of chronic inflammation including scars and chronic ulcers. When an SCC develops within a chronic wound it is known as a Marjolin's ulcer.[17] The incidence of SCC usually increases significantly after age 60, Precursors to SCC include actinic keratosis and SCC in situ, which is also known as Bowen's disease.[17]

c. Basosquamous carcinoma (BSC)

BSC, also known as a metatypical BCC, is a tumor that has histologic features of both a BCC and a SCC. These malignancies tend to behave more like SCC's in that they are more aggressive and have a greater likelihood of both metastasizing and recurring after treatment.[17]

d. Malignant vascular tumours

Malignant vascular tumours are vascular neoplasms arising from endothelial cells, with the majority being sarcomas.[18] Kaposi sarcoma (KS) and angiosarcoma fall within this group.

KS is a low-grade vascular tumour associated with infection with human herpes virus 8 (HHV-8) and can develop both within the dermis and internal organs.[19] There are four major types of KS namely Classic, African endemic, Iatrogenic immunosuppression and acquired immune deficiency syndrome (AIDS)-related. The latter is by far the most commonly seen in SA and is considered an AIDS-defining illness,[20] with a variable clinical course, ranging from minimal disease to a rapidly progressing malignancy that can result in significant morbidity and mortality.[19] **Angiosarcoma** is an aggressive neoplasm that tends to develop on the face or scalp of elderly individuals. It has a poor prognosis with less than 15% of patients surviving five years.[21] Risk factors for its development will be expanded upon in section 1.2.3.

e. Primary cutaneous lymphomas

Primary cutaneous lymphomas can be divided into primary cutaneous T-cell lymphomas (CTCL) and primary cutaneous B-cell lymphomas, comprising 75% and 25% respectively. CTCL's are a group of neoplasms of skin-homing T-cells.[22] **Mycosis Fungoides** is the most common type of CTCL and comprises about half of all primary cutaneous lymphomas. It is a low-grade lymphoma characterized by a protracted course clinical course, typically progressing from the patch stage to plaque to tumour stage.[22]

f. Malignant adnexal neoplasms

This group of malignant tumours exhibits differentiation towards a type of cutaneous adnexal epithelium, namely the pilosebaceous unit, eccrine or apocrine sweat glands. It includes the sebaceous carcinoma, pilomatrical carcinoma, porocarcinoma, spiradenocarcinoma, cyclindrocarcinoma and adnexal adenocarcinoma.[23]

g. Malignant fibroblastic tumours

These neoplasms represent a very large subset of mesenchymal tumours.[24]

Dermatofibrosarcoma protuberans is a locally aggressive sarcoma of intermediate malignancy that rarely metastasizes. It occurs predominantly on the trunk and proximal extremities and presents as a slow growing, firm, indurated, asymptomatic plaque.[24]

h. Malignant cutaneous neural tumours

Cutaneous neural tumors can be classified into two major groups, derived from either peripheral nerves or ectopic neural tissue.[25] **Merkel cell tumour** is an aggressive malignant neoplasm falling within the former group and frequently metastasizes to internal organs.[25]

1.2.2.2 Melanoma skin cancer

a. Cutaneous malignant melanoma

Although CMM occurs less frequently than some of the other major cutaneous neoplasms, it is significantly more dangerous if not found in the early stages and due to its metastatic potential is responsible for > 75% of deaths due to skin cancer.[26] Major subtypes of invasive CMM include superficial spreading, lentigo maligna, acral lentiginous and nodular melanoma.[26] Risk factors for CMM development are elaborated on in section 1.2.3.

1.2.3 Risk factors for skin cancer development

Risk factors for the development of NMSC and CMM can be divided into environmental exposures, preexisting pathology and genetic risk factors.

1.2.3.1 Environmental exposures

Exposure to certain environmental factors plays a major role in predisposing to skin cancer development.

a. Ultraviolet radiation

UVR exposure is the predominant cause of BCCs and cutaneous SCCs with intermittent intense exposure being the major risk factor for developing BCCs and cumulative exposure for SCC.[16,17] A

systematic review of case control studies has found a strong association between CMM, intermittent intense exposure and sunburn in childhood and adolescence.[27]

b. Tanning lamps, ionizing radiation and photochemotherapy

Tanning lamp usage and exposure to ionizing radiation increase the risk of developing NMSC.[16,17] Long-term exposure to UVA combined with the intake or application of psolaren (PUVA), increases the risk of SCC development.[17] Chronic radiodermatitis is a risk factor for angiosarcoma.[21]

c. Chemical exposures

Exposure to arsenic, pesticides and polycyclic aromatic hydrocarbons increase the risk of the developing SCC.[15]

1.2.3.2 Preexisting pathology

A variety of pathological conditions are risk factors for skin cancer development.

a. Immunosuppression

Organ transplant recipients have a markedly increased incidence of NMSC, primarily SCC, with immunosuppressive drugs including calcineurin inhibitors and azathioprine increasing the risk of their development.[28] Immunosuppression is also a risk factor for developing angiosarcoma.[21]

b. Viral Infections

Human immunodeficiency virus (HIV) infection increases the risk of developing NMSC by 3-5 fold.[29] Both CMM and SCC have a more aggressive course in patients with HIV.[30]

HHV-8 causes KS, which is 50 times more likely to develop in individuals infected with HIV.[29] Fortunately, the introduction of antiretroviral therapy (ART) has helped to decrease the incidence, mortality and morbidity associated with HIV-associated KS in SA.[31]

Human papilloma virus (HPV) subtypes, namely HPV 16, 5, and 8 act as co-carcinogens in conjunction with UVR exposure in the early development of SCC.[28]

Merkel cell polyomavirus is the cause of most Merkel cell carcinomas.[25]

c. Chronic inflammation

There is an increased risk of cutaneous SCC developing in chronically inflamed skin as a result of burns, scars and chronic ulcers.[17]

d. Lymphoedema

Chronic or congenital lymphoedema is a risk factor for the development of angiosarcoma.[21]

e. Nevi

Individuals with >5 atypical nevi or >100 typical nevi are at higher risk for developing CMM.[32]

1.2.3.3 Genetic risk factors

Hereditary factors and gene mutations may predispose to the development of skin cancer.

a. Genetic predisposition

Phenotypic characteristics such as red or blonde hair, light skin pigmentation, freckling, little ability to tan and light eye colour are risk factors for NMSC and CMM,[17, 26] whilst 10% of melanomas are familial.[33] Angiosarcoma of the face or neck occurs significantly more commonly in elderly White population groups.[21]

b. Genetic syndromes associated with increased risk

Xeroderma pigmentosum and oculocutaneous albinism (OCA) heighten the risk of developing NMSC. Patients with epidermodysplasia verruciformis and dystrophic epidermolysis bullosa are also at risk of developing SCC, while those with Nevoid basal cell carcinoma syndrome and Bazex syndrome are at high risk of developing BCC.[16, 17]

1.2.4 A global perspective on skin cancer incidence

Annual skin cancer incidence is determined by the number of histologically confirmed new primary cutaneous malignancies occurring over a one-year period of time.[34] Over a number of years trends in incidence can be calculated. A recent systematic review of the worldwide incidence of NMSC, has found an increase in its incidence globally.[8] NMSC incidence varies widely, with the highest rates in Australia and the lowest in parts of Africa. The incidence of BCC in Europe is increasing at a rate of 5% per year, while in the United States of America an annual increase of 2% is apparent.[8] Due to intermittent UVR exposure being more critical than total UVR exposure in the aetiology of BCC, those exposed to long-term UVR, as is the case in some subgroups of the Australian population, have an increased likelihood of developing SCC than those in regions like the United Kingdom (UK), where

intermittent exposure is more frequent. This is reflected by the BCC: SCC ratio, which in Australia is approximately 5: 2 and in the U.K. is 4: 1.[8]

The incidence of CMM is increasing at 3-7% per year in fair-skinned populations globally,[9]while in Black and Asian populations it remains low in comparison.[35] However, in Black patients, the five-year relative survival rate is lower than in the White population, which may be due to delayed diagnosis related to a perceived lower risk and to atypical locations of CMM in nonexposed areas.[36] The dermoscopic features of a melanoma do not differ between dark and light-skinned individuals, thus identification of a suspicious lesion in a person of colour, should not pose an obstacle to the trained eye.[37] Clark level and Breslow depth describe the anatomical involvement and depth of invasion of a CMM respectively.[38] (Appendix 1& 2) Tumour thickness is an indicator of the effectiveness of early detection of melanomas. In many countries there is an on going trend toward early detection and therefore thinner melanomas being detected, while the percentage of melanoma seen insitu has increased.[39]

1.2.5 Skin cancer in Sub-Saharan Africa

In Sub-Saharan Africa (SSA), the highest incidence rates of NMSC have been found in Zimbabwe and SA, which have a higher proportion of light skinned individuals than the other African countries.[34] The frequency of cutaneous malignancies among darkly pigmented individuals of the developing world is much lower,[40] but the true occurrence is yet to be fully characterized, as under-reporting especially from SSA, is highly likely.[29] The reports that have been compiled thus far indicate that both SCC and KS rank among the top ten most frequent malignancies in these populations, and that SCC is the most common skin cancer in Black Africans and African Americans.[29] Chronic ulcers and scars are the major risk factors for SCC in black individuals.[41] SCC due to a chronic ulcer has a 30% metastasis rate in comparison to the 2-4% metastasis rate in SCC associated with exposure to solar UVR.[37] This may explain the poorer outcomes observed in black patients with SCC.[42]

In contrast to White populations where 90% of CMM's develop on sun-exposed skin, 60% of CMM in Black Africans are found on unexposed sites, with acral lentiginous melanoma (ALM) being the most common histological subtype.[43] Trauma has been speculated as a possible aetiological factor in the plantar predilection of CMM in Black African individuals but additional research is required in this regard.[44] Socioeconomic factors influence disease outcomes of CMM and less affluent groups tend to be diagnosed with more advanced disease and hence poorer survival rates.[44]

Individuals with OCA have impaired formation of the UV-protective pigment called melanin. OCA is a known risk factor for developing skin cancer, with SCC developing most frequently while CMM is rare.[45] The risk of an African individual with OCA developing SCC in contrast to the general public has been reported to be as high as up to 1000 fold.[46] A high rate of OCA is found in some African ethnic groups such as the Tonga tribe in Zimbabwe which has a frequency of 1/ 1000.[47]

1.2.6 Skin cancer in South Africa

South Africans are particularly susceptible to skin cancer due to their exposure to year-round high ambient solar UVR.[5] In a population of 54 million, the ethnic mix within SA shows a diverse population, consisting of Black (80.2%), White (8.4%), Coloured (8.8%) and Asian/Indian (2.5%) population groups.[48] The incidence of NMSC in White South Africans, was found to be four fold higher than rates in the UK and France.[49] The outcome of a survey of all histologically confirmed cases of skin cancer (n=44,716) that were reported to the National Cancer Registry (NCR) between 2000 and 2004 are illustrated in Table 1.[50]

Table 1. Mean annual age-standardised incidence of reported BCC, SCC and CMM per 100,000 persons in SA, 2000-2004[50]

Type of carcinoma	Black	Asian/Indian	Coloured	White
BCC	4.7	13	85.7	311.1
SCC	4.6	7	41.5	101.3
CMM	2.2	1.8	10	37

The White population had the highest reported incidence of all three skin cancers, followed by the Coloured, then Indian/Asian and Black populations. Although in comparison, age standardised incidence rates were low in Indian/Asian and Black population groups, they were still higher than those found in other African countries.[34] The reason for this is thought to be due to their fairer skin, in relation to the darker skin of individuals found in the rest of the continent.[34] As Black individuals comprise 80% of the SA population, even the low rates of SCC, BCC and CMM in this group, may be consequential in terms of the national health burden.

HIV infection increases the risk of NMSC and SA has one of the world's largest HIV epidemics, with 11,2% of the population (6.19 million individuals) being HIV positive.[3, 29] Thus it can be inferred that HIV has played a role in increasing NMSC incidence in the country. Fortunately 42% of HIV infected South Africans have been initiated on ART and a recent meta-analysis has shown that these individuals have a lower risk of developing NMSC than those not initiated on treatment (standardised incidence ratio, 95% confidence interval; 1.95 [1.10-3.47] versus 2.11 [1.44-3.12]). [51, 52]

Although completely accurate South African skin cancer data is not available after 2004 (see section 1.28 below), the estimated yearly incidence of CMM in 2014 was 4.76 per 100,000 persons overall and 19.2 per 100,000 in whites.[53] A comparative study conducted in SA concurred with previous observations in the literature and found a poorer prognosis for CMM in dark skinned individuals, with a 20% and 42% five-year survival rate in blacks and whites respectively.[54] The cause for this has been attributed to the late presentation commonly observed in the Black population, in whom the most common subtype is ALM. This subtype has a poorer prognosis due to depth of invasion at diagnosis, with a five-year survival rate of less than 50%.[29]

1.2.7 Current initiatives to combat skin cancer in South Africa

Two recent and promising South African skin cancer prevention initiatives are the Skin Cancer Foundation of South Africa (SCFSA) and the Nivea Sun Smart programme. The SCFSA was launched at the end of 2013 and is an independent, self-funded organisation, dedicated to preventing skin cancer

by increasing public awareness.[55] It has implemented a national skin cancer screening day on the 1st of September each year, on which South Africans can be screened free of charge for skin cancer by a Dermatologist. The Nivea Sun Smart programme has been operating in the KwaZulu-Natal province since 2014, and provides age-appropriate education on sun protection at junior and high schools.[56] It also offers a service installing sunscreen dispenser units at schools and refilling them monthly. In addition, SA has the largest antiretroviral treatment programme globally which is also helping to decrease the risk of skin cancer development in HIV positive persons.[51]

1.2.8 The need for up-to-date skin cancer statistics

Within White populations, NMSC has the highest incidence of all cancers,[8] in spite of this it is seldom included in national cancer statistics around the world, with very few publications reviewing incidence rates in each country. Although NMSC does have a low mortality rate, it may impact affected persons' quality of life, and is putting a large financial burden on health care services. In the UK, updates to the National Institute for Clinical Excellence (NICE) guidelines have highlighted the need to assess the true epidemiology of NMSC and to bring skin cancer registration in line with other malignancies, to enable accurate prevention studies to be conducted on the effects of sun protection.[57] The findings drawn from the data on skin cancer incidence are beneficial for a number of reasons including:

a. Detection of changes in cancer patterns

Changes in the cancer patterns previously observed in SA can be expected. This is because the incidence of NMSC is increasing globally and SA has a large population of HIV infected individuals, which increases the risk of NMSC and KS.[29, 58]

b. Enabling the monitoring of skin cancer cumulative incidence (CI) at provincial and national levels

The incidence of CMM and NMSC in the South African White population already ranks among the highest in the world.[8, 59] Despite occurring much less frequently, both BCC and SCC are ranked among the top ten malignancies in Black African males.[34] Increased life expectancy due to improved standards of living, progressive ozone depletion and westernisation of social and behavioural attitudes are all

expected to increase the burden of skin cancer in SA in the 21st century.[59] Taking into consideration the high incidence that currently prevails and the predications that this incidence is likely to rise further, it seems prudent to monitor incidence levels provincially and nationally.

c. Provision of a framework to measure the effectiveness of currently implemented skin cancer prevention programmes

Accurate up-to-date statistics for a few years continuously, make it possible to identify trends in incidence. A decreasing trend in skin cancer incidence may provide proof that skin cancer prevention programmess are being effective.

d. Encourage increased government allocation of financial resources towards developing sustainable skin cancer prevention policies and strategies

In Australia, primary prevention strategies, such as the SunSmart programme that was implemented in the early 1980's, only began having effects on reducing incidence twenty years later, due to risk of developing NMSC being related to a number of lifelong factors.[8] This should encourage the government to act timeously and allocate adequate finances towards the development of skin cancer prevention strategies.

e. Help to ensure the adequate allocation of financial resources to diagnose and treat skin cancer

A cost-of-illness study was performed in 2015 to measure the economic burden of skin cancer in SA. The estimated total annual cost of treating skin cancers in SA was ZAR92.4 million.[60] Provision will need to be made for this sizeable cost to the already strained healthcare budget.

f. Promotion of increased awareness among medical practitioners

Skin cancer incidence studies may help to make medical practitioners more aware of how common certain cutaneous malignancies are, as well as what age and population groups are at increased risk and thus warrant careful, frequent examination. It may also help to increase cognisance that dark-skinned individuals are also susceptible to developing skin cancer. This is important as pigmented

lesions are difficult to examine in dark skin and may initially be missed, which could result in late commencement of treatment. Additionally, published data on skin cancer incidence may help to raise awareness that HIV increases the risk of developing NMSC and thus suspicious lesions in these patients must not be overlooked.

Cancer statistics in SSA are generally scanty and therefore unreliable due to a lack of functional population based cancer surveillance systems and national registries.[61] The development and progress of the South African NCR was hampered from 2005-2010 by a lack of funding, shortages of relevant manpower and decreased private sector submissions following concerns regarding patient confidentiality. These limitations resulted in the NCR being unable to capture, code, and analyse the available or required data and led to a ten-year backlog of incidence reports.[10] In 2011, the South African Department of Health created Regulation No 380 of the National Health Act (Act 61 of 2003), which made cancer a reportable disease.[62] This differs from a notifiable condition, which relates to disease outbreaks where timing is critical to public health and therefore the healthcare provider has a limited time in which to report the case.[63] The new act will require all histologically confirmed cases of cancer to be reported to the NCR within three months.[62] In addition to this landmark event, the repositioning of a cancer surveillance system as a national health priority, supported by stable NCR leadership and extended collaborations have enabled the NCR to become fully operational,[10] resulting in the 2010 cancer report having been recently published, albeit without all private sector data.[64] The NCR has expressed the view that cancer incidence in SA is under-reported due to the lack of a comprehensive cancer surveillance system. Thus over the next ten years it is committed to developing a network of independent population-based cancer registries based in a variety of clearly defined districts. The heterogeneous catchment populations will be representative of the ethnic and geographical diversity of the South African population. Each registry will report annually to the NCR to provide a reliable and comprehensive indication of cancer incidence for the entire country.[10] Their aim is to publish cancer incidence data for SA, within a worldwide-accepted lag period of 3–5 years.[65] These plans are opportune, as concern has been expressed that if incidence rates continue to rise unchecked, skin cancer may begin to represent a major health problem and a significant burden to the South African private and

public health sectors.

1.2.9 Aim and objectives

The study aimed to describe the nature and extent of different types of histologically confirmed skin cancers presenting in the public and private health sectors of the NC province from 1st January 2008 to 31st of December 2012.

The objectives were to conduct a retrospective chart review of histologically confirmed new primary cutaneous malignancies from 1/1/2008 to 31/12/2012 on cases in the DISA, PathCare and Ampath databases. The different types of skin cancer, quantity of each and the distribution of the five commonest invasive malignancies by population group, age, gender, anatomical site and health sector were explored. The CI of the five commonest invasive malignancies and their trends over five-years were calculated. Trends in melanoma thickness over five years were explored.

This is the first South African study to collate and analyse public and private skin cancer data for an entire province. The study provides insight into the skin cancer burden faced by the NC Province and may give an indication of the skin cancer problem in SA at large. It provides a basis to allow for future monitoring of skin cancer incidence at a provincial level, and may aid in detecting changes in cancer patterns in the future. It may assist in providing a stimulus for the development of appropriate policies on cancer prevention, and may help to increase government allocation of financial resources towards developing sustainable prevention strategies. It may also provide a framework to measure the effectiveness of newly implemented skin cancer prevention programmes.

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Chapter 2: Publication ready manuscript

Primary cutaneous malignancies in the Northern Cape Province of South Africa: a retrospective histopathological review

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Abstract
Background: Excessive sun exposure and high human immunodeficiency virus prevalence increase skin cancer risk in South Africa.
Objective: To describe the nature and extent of skin cancers presenting in public and private health sectors of the Northern Cape Province.
Methods: A retrospective analysis of histologically-confirmed new primary cutaneous malignancies from 1/1/2008 to 31/12/2012 was conducted using public and private health sector databases. Types, quantity and distribution of common invasive malignancies by population group, age, gender, anatomical site and health sector were explored. One-year cumulative incidence was calculated and logistic regression models used to analyse incidence and melanoma thickness trends.
Results: 4270 biopsies (14 cutaneous malignancies) were identified. Most common were Squamous Cell Carcinoma (SCC), Basal Cell Carcinoma (BCC), Kaposi Sarcoma (KS), Cutaneous Malignant Melanoma (CMM) and Basosquamous carcinoma. The odds of a White male developing SCC increased by 8% each year (OR: 1.08; CI: 1.01-1.15; p-value: 0.022) whilst the odds of a Black male developing SCC and KS decreased by 9% (OR: 0.91; CI: 0.84-0.99; p-value: 0.033) and 18% (OR: 0.82; CI: 0.70-0.97; p-value: 0.022) each year, respectively. SCC and CMM were diagnosed at more advanced stages within public versus private sectors. CMM is being detected earlier, as indicated by low stage depth increasing by 72% annually (OR: 1.72; 95% CI: 1.04 -3.01; p-value: 0.042).
Conclusion: Results suggest that reported skin cancer patterns are changing. There is a need for further research and equitable appropriation of financial resources and effort toward developing primary skin cancer prevention initiatives in South Africa.

Keywords:
cutaneous malignancy, Northern Cape, skin cancer, retrospective, histology, South Africa.

Introduction

Due to its location, most parts of South Africa (SA) have high levels of solar ultraviolet radiation (UVR).[1] Despite its geographical size, the Northern Cape (NC) Province has the smallest population, with only 1.18 million inhabitants. [2] Its economy relies mainly on mining and agriculture and almost one fifth of the currently employed NC population work outdoors within the agricultural industry.[3] Approximately 90% of non-melanoma skin cancer (NMSC) is attributable to personal UVR exposure and thus South Africans are especially susceptible to skin cancer due to their year-round exposure to high ambient solar UVR.[4] Individuals working in outdoor occupations are at an even greater risk of NMSC, as they are likely to be outside for more daylight hours.[5, 6] SA has one of the world's largest human immunodeficiency virus (HIV) epidemics,[7] with infected individuals having a 3-5 fold and 50 fold increased risk of developing NMSC and HIV-associated Kaposi Sarcoma (KS), respectively.[8]

Incidence of NMSC and cutaneous malignant melanoma (CMM) is increasing globally, thus reporting systems to monitor number of cases and trends over time are essential.[9, 10] However, due to limited private sector submissions to the National Cancer Registry (NCR), the last comprehensive data inclusive of all health sectors was published in 2004, making it difficult to establish whether skin cancer incidence in SA has followed the global trend.[11]

In 2011, the South African Department of Health passed a regulation,[12] which made cancer a reportable disease, requiring all histologically-confirmed cases be reported to NCR.[13] Concerns have been raised that if skin cancer incidence continues to rise unchecked, it may become a major health problem and place a large financial burden on private and public health services. Of additional concern is that melanomas of depth greater than 4mm carry a high risk of mortality. [14, 15]As tumour thickness provides an indication of how early a melanoma has been detected, monitoring trends in melanoma thickness to assess whether thinner melanomas are being detected may be appropriate.[16] This study aimed to describe the nature and extent of different types of histologically-confirmed skin cancers presenting in the public and private health sectors of the NC province to provide insight into the local skin cancer burden in SA.

Methods

A retrospective chart review of histologically-confirmed new primary cutaneous malignancies from the 1st of January 2008 to the 31st of December 2012 was conducted. Different types of skin cancer, quantity of each and the distribution of the five commonest invasive malignancies by population group, age, gender, anatomical site and health sector were explored. The incidence of the five commonest invasive malignancies and their trends over five years were calculated. Trends in melanoma thickness were analysed.

Skin biopsies from public facilities within the NC are sent to the National Health Laboratory Service (NHLS) histopathology laboratory, while those from private facilities are sent to either PathCare or Ampath laboratories. Data on all incident cases was extracted by performing a Systemised Nonmenclature of Medicine (SNOMED) search of the DISA, PathCare and Ampath databases, using the SNOMED codes for all cutaneous malignancies. The data extracted from the histopathology reports for each patient included the date, histopathological diagnosis, population group, gender, age, anatomical site of the lesion, and health sector. The study was conducted in accordance with ethical principles contained in the Helsinki Declaration.[17] It was approved by the Faculty of Health Sciences Ethics Committee for the University of Cape Town. (HREC/REF: 357/2015)

All histologically-confirmed new primary cutaneous malignancies in public and private sector paediatric and adult patients, from towns within the NC and between the study dates (above) were eligible to be included. Exclusion criteria included new primary cutaneous malignancies that were not incident cases, cutaneous metastases, squamous cell carcinoma (SCC) of the tongue, palate, buccal mucosa, vagina and anus and KS of the tonsil, tongue, larynx and nasopharynx.

Statistical Analysis

Before analysisng the data, the Data Management and Statistical Analysis Unit (DMSA) of the University of the Witwatersrand used a hot-deck imputation method to correlate cases with no population group against a reference database containing surnames with a known population group. This enabled estimates of population group for each patient to be made, as was used by NCR in 1998 when they faced a similar dilemma. The method proved to be accurate and its results compared well with previous registry statistics.[18-20]

For the primary analysis two software packages were used, namely, SPSS Statistics (Version 21, IBM Corporation) and R (Version 3.1.3, 64-bit version, R Foundation for Statistical Computing). The statistical analysis was divided into three components. The first component involved establishing the main types of skin cancer with respect to patient's demographic and histological data. Empirical descriptive statistics were calculated. The Kruskal-Wallis test for similarities in age distribution between different types of cutaneous malignancies was performed as the data were not normally distributed.

The second component involved calculating the incidence of the five most common cutaneous malignancies for each year. Throughout this work incidence refers to yearly cumulative incidence which is the proportion of those at risk who acquire cancer over a one year period. The incidence of each malignancy was calculated using the total number of new histologically-confirmed cases of a skin cancer type in a particular year as the numerator, with the NC mid-year population estimate for the year as the denominator. This was reported as incidence per 100 000/year.

The third component investigated trends in incidence and melanoma thickness over the five years. Logistic regression modelling was used to estimate annual incidence trends controlling for potential confounders. The Hochberg procedure was used to adjust for multiple comparisons. The level of significance was set at a two-sided p-value ($p < 0.05$). To investigate trends in melanoma thickness over five years, the Clark's staging data was collapsed into "High stage" and "Low stage" categories for analysis. "Low stage" included Clark's levels 1 and 2, and "High stage" included Clark's levels 3 to 5. Odds ratios (ORs) for a low stage were estimated using logistic regression modelling adjusted for potential confounders.

Results

4270 biopsies comprising 14 cutaneous malignancies were identified. The five most common invasive malignancies made up 82.7 % of all the cases. In descending order they were: SCC, basal cell carcinoma (BCC), KS, CMM and Basosquamous carcinoma (BSC) (Table 1).

Table. 1 Skin cancer spectrum and distribution

	Skin cancer types	n	%
1	squamous cell carcinoma	1938	45.4
2	basal cell carcinoma	1185	27.8
3	squamous cell carcinoma insitu	667	15.6
4	kaposi sarcoma	276	6.5
5	cutaneous malignant melanoma	101	2.3
6	basosquamous carcinoma	43	1
7	cutaneous malignant melanoma insitu	34	0.8
8	dermatofibrosarcoma protuberans	13	0.3
9	mycosis fungoides	3	0.07
10	sebaceous adenocarcinoma	3	0.07
11	trichilemmal carcinoma	3	0.07
12	angiocentric T cell lymphoma	2	0.05
13	merkel cell carcinoma	1	0.02
14	mucinous carcinoma	1	0.02
	Total	4270	100

Demographics of the five most common invasive skin cancers

Population group distribution comprised 2093 (52%) White, 1047 (26%) Black, 864 (21.4%) Coloured and 23 (0.6%) Indian/Asian patients. Imputed population group was unspecified in 243 patients. BCC, CMM and BSC occurred relatively more frequently in White individuals than in other population groups. A high rate of SCC was observed within White, Black and Coloured individuals. KS occurred more commonly within the Black population (Figure 1).

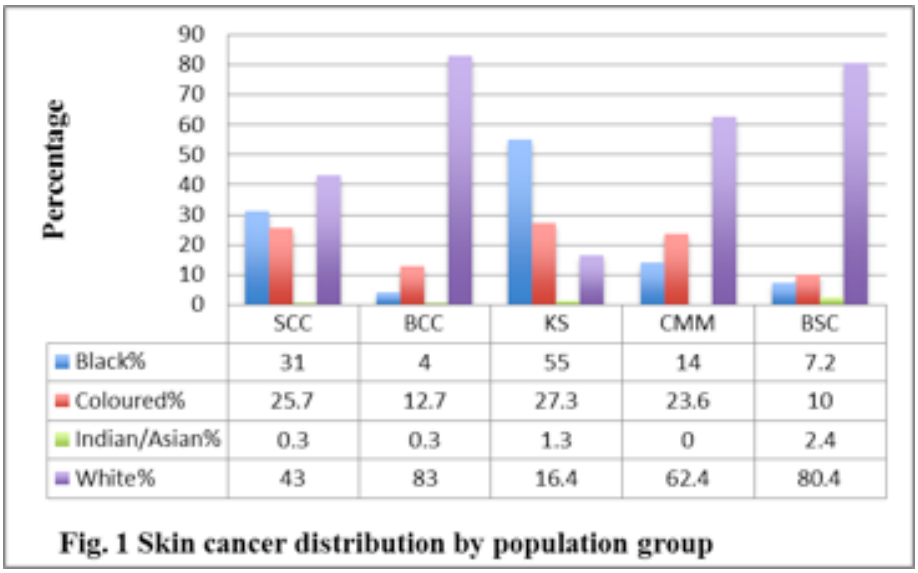

Fig. 1 Skin cancer distribution by population group

Male/female ratio was 1:1 (2108 males, 2095 females). Gender was unspecified in 67 patients. All five of the most common invasive cutaneous malignancies affected males more frequently than females, with BSC occurring twice as often in males. Squamous cell carcinoma in situ (SCCI) represents the major exception to this trend, occurring six times more frequently in females.

Age range spanned 2 -101 years with a mean age of 51.6 years. There was a statistically significant difference in age distribution between malignancies ($p < 0.001$). BCC occurred most frequently in the age group 60-69 years, while CMM and SCC presented most commonly in those aged 50-59 years and BSCs in those aged 70-79 years. The majority of KS occurred in the younger age group 30-39 years.

Head and neck regions were the most common anatomical sites affected by BCC, SCC and BSC. CMM occurred most commonly overall on the lower limb with the trunk and lower legs being most frequently affected in men and women, respectively.

Of the 4270 biopsies, 2448 (57%) and 1822 (43%) were from the public and private healthcare sectors, respectively. In decreasing order of frequency BCC, SCC and CMM occurred most frequently within the private sector while SCC followed by KS accounted for the majority of the pathology within the public sector (Figure 2). Ninety percent (n=1061) of the BCCs occurred within private sector patients, while 73% (n=1417) of SCCs identified were from the public sector. Of the 101 patients with CMM, 62% (n =63) were from the private sector while 38% (n=38) were from the public sector. 84% of the private sector patients were White, while within the public sector 27% were White, 43% were Black and 29% were Coloured (Table 2).

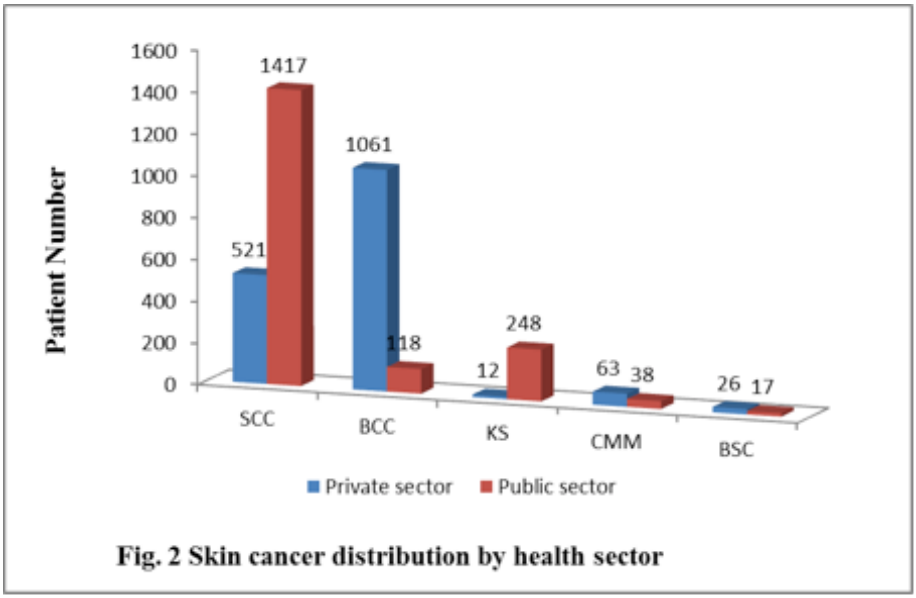

Fig. 2 Skin cancer distribution by health sector

Table 2. Population group distribution within private and public sectors

Population group	Private sector (n)	% of Private sector	Public sector (n)	% of Public sector
Black	71	4	976	43
Coloured	199	11.7	655	29
Indian	5	0.3	18	1
White	1473	84	620	27
Total	1822	100	2448	100

1524 (79%) of patients with invasive SCC could be categorised according to tumour differentiation. Of these, 21% were well-differentiated, while 59% were moderately-differentiated and 20% were poorly-differentiated. In both the Coloured and Black populations almost one quarter of malignancies were poorly differentiated.

Incidence and five-year incidence trends

Table 3 reports the incidence of the five most common invasive cutaneous malignancies per 100 000, from 2008 to 2012, as well as the estimated ORs of each cancer for a one-year increase. Incidence was then plotted and logistic regression was used to model trends. Categories in bold type in Table 3 are those in which a significant trend was seen (Figure 3).

Table 3. Incidence of malignancies from 2008-2012 and estimated OR's for a one-year time increase

CA	Gender	Race	Incidence per 100 000/year					Odds ratio			p-values	
			2008	2009	2010	2011	2012	Est	95% CI LL	95% CI UL	Adj	Unadj
SCC	F	B	19	19.6	13.8	18.5	15.6	0.96	0.88	1.04	0.9852	0.2787
		C	17.3	19.7	19.7	34.6	16	1.05	0.96	1.15	0.9852	0.2731
		W	142.2	143.4	145.2	186.6	115	1	0.92	1.08	0.9852	0.9429
	M	B	18.3	21.9	17.5	17.1	12.6	**0.91**	**0.84**	**0.99**	**0.9074**	**0.0336**
		C	19.2	24.8	23.4	21.35	23.5	1.02	0.93	1.12	0.9852	0.6523
		W	215	158.3	230	248.7	248	**1.08**	**1.01**	**1.15**	**0.6308**	**0.0225**
BCC	F	B	0.3	0.6	1.47	0.84	0.63	1.13	0.76	1.70	0.9852	0.5456
		C	5.7	3.9	4.8	6.9	6.1	1.06	0.89	1.27	0.9852	0.4851
		W	157.7	108.6	166.6	171.1	185	1.08	1	1.16	0.9852	0.0532
	M	B	2.1	1.8	1.6	1.86	2.9	1.09	0.85	1.41	0.9852	0.5189
		C	6.1	8.9	6.3	11.9	8.3	1.09	0.94	1.27	0.9852	0.2709
		W	295	208	327.5	346.1	295	1.05	0.99	1.11	0.9852	0.0756
KS	F	B	3.93	4.22	4.12	2.53	2.22	0.86	0.71	1.04	0.9852	0.1138
		C	4	2.63	2.4	2.47	1.29	0.80	0.60	1.46	0.9852	0.0998
		W	8.19	4.34	7.14	8.19	7.5	1.03	0.72	1.46	0.9852	0.8858
	M	B	5.98	7.55	2.93	5.59	2.26	**0.82**	**0.70**	**0.97**	**0.6308**	**0.0222**
		C	3.55	1.87	2.44	7.29	2.3	1.08	0.85	1.37	0.9852	0.5243
		W	12.5	6.25	12.5	7.69	9.75	0.97	0.70	1.32	0.9852	0.8328
CMM	F	B	0.61	0.60	0.58	0.28	0.63	0.95	0.58	1.52	0.9852	0.8186
		C	0.44	0.43	1.92	0	0.43	0.94	0.54	1.59	0.9852	0.8107
		W	11.1	4.34	14.2	4.4	25	1.26	0.95	1.70	0.9852	0.1130
	M	B	0.35	0.35	0	0.31	0	0.68	0.24	1.55	0.9852	0.3836
		C	1.01	2.81	1.95	1.04	0.46	0.81	0.55	1.16	0.9852	0.2578
		W	12.5	16.6	15	17.9	17.1	1.07	0.83	1.36	0.9852	0.6109
BSC	F	B	0	0.3	0	0	0	0.56	0.04	2.54	0.9852	0.5037
		C	0.44	0	0.48	0	0	0.58	0.17	1.35	0.9852	0.2631
		W	2.22	2.17	9.5	2.22	5	1.15	0.72	1.88	0.9852	0.5620
	M	B	0	0	0	0.62	0	1.72	0.60	8.83	0.9852	0.3730
		C	0.51	0	0	0	0.46	0.99	0.34	2.89	0.9852	0.9852
		W	5	6.25	12.5	12.8	21.9	**1.45**	**1.08**	**1.99**	**0.5299**	**0.0177**

Categories in **bold type** are those in which a significant trend was seen
CA: cancer, Est: estimated odds ratio, 95% CI LL: 95% confidence interval lower limit, 95% CI UL: 95% confidence interval upper limit, Adj: adjusted p-value, Unadj: unadjusted p-value, SCC: squamous cell carcinoma, BCC: basal cell carcinoma, KS: kaposi sarcoma, CMM: cutaneous malignant melanoma, BSC: Basosquamous carcinoma, F: female, M: male, B: Black, C: Coloured, W: White
*The Hochberg procedure was used to adjust for multiple comparisons. This step-up procedure may result in a number of adjusted p-values being of the same value and as implemented in the R function 'adjust p'.

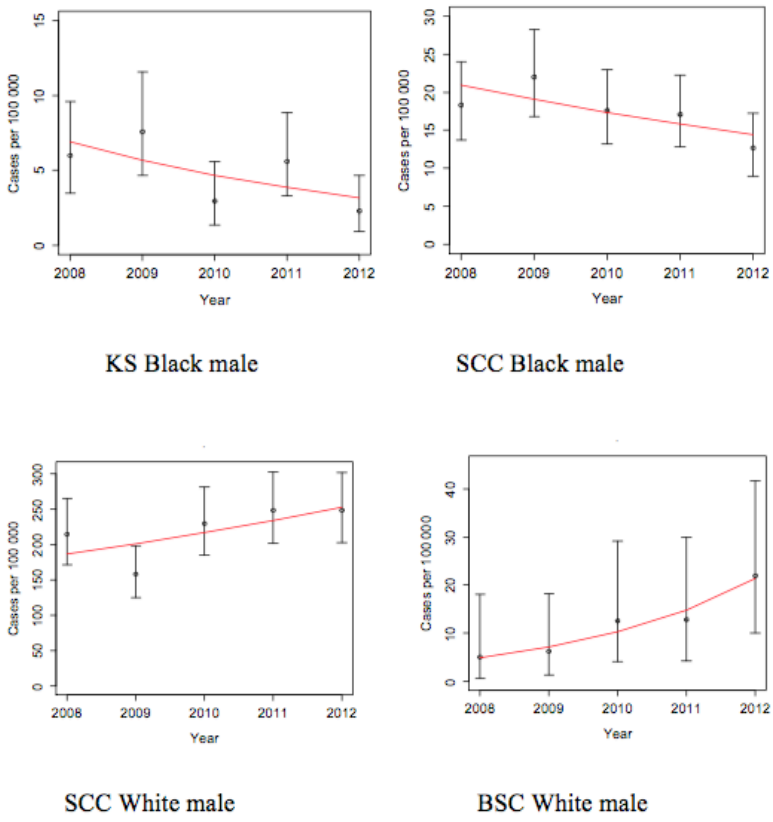

Fig. 3 Significant changes in incidence trends from 2008 - 2012

The odds of a Black male developing KS or SCC decreased by 18% (OR: 0.82; CI: 0.70-0.97; p-value: 0.0222) and 9% (OR: 0.91;CI: 0.84-0.99; p-value: 0.0336) respectively, every year over the five-year period. In contrast, the odds of a White male developing BSC or SCC increased by 45% (OR: 1.45; CI: 1.08-1.99; p-value: 0.0177) and 8% (OR: 1.08; CI: 1.01-1.15; p-value: 0.0225) respectively. Once the Hochberg procedure was applied, significant trends in incidence were not observed.

Trends in melanoma thickness

55% of CMMs were not sub-typed and 25% were still in the insitu phase at the time of excision. Acral lentiginous melanoma (ALM) was the sub-type that occurred most frequently and all cases of this sub-type occurred within the public sector. Clark level for CMM within the private sector ranged from 1 - 4 (mean: 2.7) while in the public sector it ranged from 2 - 5 (mean: 4.2). Only in 2012 were no cases with a Clark level 5 seen. Once Clark's staging data were collapsed into low and high stages and a logistic regression model was applied, the OR for low stage depth for every one-year increase from 2009 to 2012 was estimated to be 1.72 (95% CI: 1.04 -3.01; p-value: 0.0429). This indicates that the odds of a low stage depth increased by 72% from one year to the next, which confirms that CMM is being detected earlier.

Discussion

SCC, BCC, KS and CMM were the four most frequently occurring skin cancers in the NC Province in accordance with the 2004 national statistics published by NCR.[21] SCC was the most frequent cutaneous malignancy seen between 2008 and 2012 and high rates were observed within White, Black and Coloured population groups. SCC incidence has risen worldwide over the past several decades at an estimated 3-10% per year.[22] The vast majority of NMSC is attributed to personal UVR exposure and SA is located within the Southern hemisphere, which has a greater intensity of UVR compared to a Northern hemisphere site at a similar latitude.[1, 23] Another contributor may be that 18.5 % of the currently employed NC population works within the agricultural industry,[3] which is more than double the proportion of the population working in agriculture in any other province. These individuals working outdoors have a 43% and 77% higher risk of BCC and SCC, respectively.[5, 6] In addition, HIV prevalence in the NC in 2011 was 17%,[24] and individuals with this disease have an increased risk of developing NMSC.[8] The HIV status of the patients included in this study was unknown but infection with this virus may have contributed to the high observed SCC incidence.

SCC and BCC tend to occur more frequently in men,[25] and this study found this observation to be true (male to female ratio of 1.1:1 for SCC and 1.7:1 for BCC). Around 75% of SCCI occurs in women,[26] but an even higher rate (87%) was seen here.

A sharp increase in BCC incidence was seen post 60 years, but in contrast to the literature,[25] the majority of SCC developed in a younger age group (i.e. 50-59 years). The same factors that may have contributed to the higher SCC incidence seen here may also have contributed to earlier presentation of SCC observed. KS observed was most likely of acquired immune deficiency syndrome (AIDS)-related type, hence KS was used as a proxy for HIV status. The South African National HIV Prevalence, Incidence and Behaviour survey in 2012 found that women aged 30-34 years and males aged 35-39 years had the highest HIV infection rates,[27] thus it is not surprising that here the KS peak incidence occurred within the age group 30-39 years.

The population group distribution within each health sector is likely to have influenced the range of malignancies seen within them. White individuals made up the majority of private sector patients and it can be assumed that these patients would have a skin type I, II or III on the Fitzpatrick phototype classification scale.[28] This may explain the predominant pathology seen within the private sector, which in decreasing order included BCC, SCC and CMM. Black patients made up nearly half of public sector patients. SCC and KS are reportedly the most common malignancies occurring within Black patients, which may explain why these pathologies accounted for majority of skin cancer within the public sector.[29, 30]

Poorly-differentiated SCC occurred in a higher percentage of Black and Coloured individuals than White individuals. Poorly differentiated sub-types tend to occur in late presentations in which the tumour is already advanced, more likely to metastasise and has a poorer prognosis.[31] An explanation for the high frequency of this sub-type in dark skin individuals may be the lower perceived risk of skin cancer by these patients.

Between 2008 and 2012, the odds of a Black male developing KS or SCC decreased significantly. A possible explanation for this decline may be that the roll-out of antiretroviral therapy (ART) in the NC only commenced in July 2004, at which time only 6.6% of HIV positive patients requiring ART were receiving them.[32] In contrast, by 2008, 90.4% of these individuals were receiving ARTs.[32] Most of the increase in CD4 count after starting ART occurs within the first three years.[33] As the incidence of both SCC and KS are influenced by HIV and immune status, improvement in many individuals immune status following ART initiation after 2004 may explain the declining rates of these pathologies a few years later.[8] The rising incidence of BCC and SCC amongst White males between 2008 and 2012 concurs with a recent systematic review of the global incidence of NMSC, which found an increase in its incidence in White populations worldwide.[9]

No significant trend was seen in CMM incidence in all races and genders between 2008 and 2012. ALM was the sub-type most commonly observed and all cases occurred within the public sector and majority were of an advanced depth (mean Breslow depth: 4.13). A Breslow depth of greater than or equal to 4 mm has a five-year survival of 37-50%.[15] ALMs are often diagnosed at an advanced stage due to difficulty in distinguishing them from ethnic pigmentation or traumatic skin changes. In addition, most practitioners have an increased threshold for performing biopsies in acral sites due to associated delayed healing times and morbidity. CMMs within the public sector were diagnosed at a more advanced stage. Socioeconomic factors influence disease outcomes in CMM and less affluent groups generally have more advanced disease and poorer survival rates.[34] In addition to the afore-mentioned factors, longer waiting times for appointments within the public sector may impact on late diagnosis. Tumour thickness is an indicator of the effectiveness of the early detection of melanomas,[16] and in many countries there is an ongoing trend toward early detection and therefore thinner melanomas being discovered as well as an increase in percentage of melanoma insitu diagnosed.[16] The fact that one quarter of melanomas were still in the insitu phase at the time of excision and that the odds of a low stage depth were found to increase from one year to the next, confirmed that CMM within the NC is also being detected at an earlier stage.

Study limitations included using only histologically-confirmed cases of skin malignancy. Some malignancies (i.e. BCCs or KS) may have been diagnosed based on characteristic clinical features and treated without histological confirmation resulting in underestimation of the true cumulative incidence. The sparsely populated NC is a large province[35] and is bordered by Namibia, Botswana and other provinces.[35] It is plausible that some individuals living within a particular region may have sought treatment for suspicious skin lesions in nearby cities, which fall under other provinces, and this may have led to skewing of the figures. HIV status of participants included in the study was unknown. As HIV increases risk for developing a NMSC,[8] this may have influenced the incidence of NMSC observed. Very little patient history was supplied on the majority of histopathology request forms and this was a limitation in regard to SCC, as one could not distinguish whether the malignancy arose within a scar, chronic ulcer or on sun exposed skin. There are no NC skin cancer statistics to refer or compare to, thus comparisons had to be made to previous national skin cancer statistics.

Conclusions

This is the first South African study to collate and analyse public and private sector skin cancer data for an entire province. These data impart insight into the skin cancer burden faced by the NC Province and provide a basis for future monitoring of skin cancer incidence. They also supply a framework to measure effectiveness of skin cancer prevention programmes within the province. Skin cancer patterns within South Africa are changing. There is a need for the equitable appropriation of greater financial resources and effort toward developing primary prevention initiatives tailored to a South African context in order to curb further increases in skin cancer incidence.

Competing interests

The authors' have no financial or non-financial competing interests in regard to this project.

Authors' contributions

N C Dlova and A Mosam made substantial contributions to the conception and design of the study and revised the manuscript critically. K York drafted the manuscript and acquired and interpreted the data. N P Khumalo assisted with interpretation and presentation of the data and revised the manuscript critically for intellectual content. R Kassanjee implemented statistical analyses and assisited with presentation and interpretation of the results. C Y Wright and P E Kellett advised during the course of the study and C Y Wright assisted with manuscript preparation for submission.

Acknowledgements

The UCT Department of Medicine supplied funding for payment of the UCT Department of Statistical Sciences for their assistance with the statistical analysis. The authors acknowledge the support provided by the consulting service at the UCT department of Statistical Sciences. Maureen Krige is acknowledged for editing the manuscript.

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Appendices

Appendix: 1 Clark level [16]

It describes the level of anatomical invasion by a tumour.

Level 1: All tumour cells are confined to the epidermis, above the basement membrane (insitu)

Level 2: Tumour invades into the papillary dermis, beyond the basement membrane

Level 3: Tumour fills the papillary dermis and extends into the interface between the papillary and reticular dermis

Level 4: Tumour invades the reticular dermis

Level 5: Tumour has invades the subcutaneous fat

Appendix 2: Breslow depth [16]

Breslow's depth of invasion is a measurement of the depth of invasion of the lesion. It is measured vertically in millimetres from the top of the granular layer of the epidermis to the deepest point of tumour involvement. The Breslow thickness is used in the TNM staging system of a melanoma. Tumours are classified into to four categories based on the depth:

- Less than 1mm thick (95-100% five-year survival)
- Between 1mm-2mm thick (80-96% five-year survival)
- Between 2mm-4mm thick (60-75% five-year survival)
- Greater than 4mm thick (37-50% five-year survival)

Appendix 3: Faculty of Health Sciences Ethics Committee for the University of Cape Town approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492 • **Facsimile** [021] 406 6411
Email: Sumayah.ariefdien@uct.ac.**za**
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

29 May 2015

HREC/REF: 357/2015

Prof N Khumalo
Department of Dermatology
J47/89
OMB

Dear Prof Khumalo

Project Title: PRIMARY CUTANEOUS MALIGNANCIES IN THE NORTHERN CAPE PROVINCE OF SOUTH AFRICA: A HISTOPATHOLOGICAL REVIEW (Masters;-Dr K York)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above mentioned study.

Approval is granted for one year until the 28 May 2016.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the following student:-Dr Katherine York is also involved in this project

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.

Hrec/ref:357/2015

Appendix 4: National Health Laboratory Service approval

NATIONAL HEALTH LABORATORY SERVICE

Academic Affairs Research and Quality Assurance
Modderfontein Road, Sandringham, 2031
Tel: +27 (0)11 885 5388 Fax: +27 (0)11 386 6296
Fax2 mail: 086 615 1909
Email: johan.vanheerden@nhls.ac.za
Web: www.nhls.ac.za

13 June 2013

Applicant : Dr Katherine York
Institution: University of KwaZulu Natal
Department :
Address: 9 Forest Glen, 41 Elizabeth Drive, Hilton, 3245
Contact Number :
Email : kathyork20@gmail.com

Re: Approval to access National Health Laboratory Service (NHLS) data

Your application to undertake a research project titled "**Primary Cutaneous Malignancies in the Northern Cape Province of South Africa: A Histopathological Review**" using data from the NHLS database has been reviewed. This letter serves to advise that the application has been approved and the required data will be made available to you to conduct the proposed study as outlined in the submitted application.

Please note that the approval is granted on your compliance with the NHLS conditions of service and that the study can only be undertaken provided that the following conditions have been met.

- Full Ethics clearance have been obtained from an approved local Ethics Committee
- Full contact details of applicant are provided to the research office and amended protocol indicating candidate and supervisor(s) name(s), institution and department.
- Confidentiality is maintained at participant and institutional level and there is no disclosure of personal information or confidential information as described by the NHLS policy.
- A final report of the research study and any published paper resulting from this study are submitted to the NHLS Academic Affairs and Research Office and the NHLS has been acknowledged appropriately.

Please note that this letter constitutes approval by the NHLS Academic Affairs, Research and Quality Assurance. Once all requirements have been met, please complete and sign the attached data request form. This should be submitted to Helpdesk4@nhls.ac.za for processing by the Corporate Data Warehouse. Any data related queries may be directed to Sue Candy, manager NHLS Corporate Data Warehouse, Tel: (011) 386 6036. Email: sue.candy@nhls.ac.za.

Yours sincerely,

Dr Johan van Heerden
Executive Manager: NHLS Academic Affairs, Research and Quality Assurance

Appendix 5: PathCare approval

PathCare
Drs Dietrich, Voigt, Mia
Vennote • Partners

PathCare Park
Private Bag X106
N1 City
7463

Tel: (27 21) 596 3400
Fax: (27 21) 596 3704
Vat Reg. No. 4600103826

Dear Dr York,

PRIMARY CONTANEOUS MALIGNANCIES IN THE NORTHERN CAPE PROVINCE OF SOUTH AFRICA: A HISTOPATHOLOGICAL REVIEW

PathCare would be willing to assist in providing anonymised data on the above according to the specifications you have provided, namely:

- Age
- Sex
- Population group
- Anatomic site

Kind regards,

John Douglass

PathCare CEO

Appendix 6: Ampath approval

PATHOLOGY LABORATORY SUPPORT SERVICES

AMPATH TRUST

AMPATH

166 Witch-Hazel Avenue, Highveld Technopark,
Centurion, 0157
Private Bag X9, Highveld, 0169
Tel: (012) 678-1000
Fax: (012) 678-1815

Registration No.: IT190/92

SERVICING DRS DU BUISSON, KRAMER, SWART, BOUWER Inc./Ing.

13 June 2013

University of Kwazulu-Natal
Research Office
Biomedical Research Ethics Administration
Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000

To whom it may concern

Research Project - Primary Cutaneous Malignancies in the Northern Cape Province of South Africa: A Histopathological Review

We wish to confirm that Ampath is aware of the above mentioned research study which will be conducted by Dr Katherine York. We are in approval of Dr York using our data on an anonymous basis protecting patient confidentiality for this purpose and according to the protocol supplied by Dr York subject to approval by your ethics committee.

We wish Dr York the best of luck with her research study.

Yours sincerely

Dr J van Rooyen
CEO

Appendix 7: South African Medical Journal, instructions to authors

SAMJ The South African Medical Journal
Leading research impacting clinical care in Africa

Author Guidelines

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.

AUTHORSHIP

Named authors must consent to publication. Authorship should be based on: (i) substantial contribution to conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual content; or (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**).

CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

RESEARCH ETHICS COMMITTEE APPROVAL

Provide evidence of Research Ethics Committee approval of the research where relevant.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to **www.icmje.org**.

ETHNIC CLASSIFICATION

References to ethnic classification must indicate the rationale for this.

MANUSCRIPTS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.
Research articles (previously 'Original articles') not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to clinical medicine and related fields. Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results,* and *Conclusion.*
Scientific letters will be considered for publication as shorter ***Research articles***.
Editorials, Opinions, etc. should be about 1000 words and are welcome, but unless invited, will be subjected to the *SAMJ* peer review process.
Review articles are rarely accepted unless invited.
Letters to the editor, for publication, should be about 400 words with only one illustration or table, and must include a correspondence address.
Forum articles must be accompanied by a short description (50 words) of the affiliation details/interests of the author(s). Refer to recent forum articles for guidance. Please provide an accompanying abstract not exceeding 150 words.
Book reviews should be about 400 words and must be accompanied by the publication details of the

book.
Obituaries should be about 400 words and may be accompanied by a photograph.
Guidelines must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed. A structured abstract not exceeding 250 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2. etc.) and summarised in a Table of Contents. References, appendices, figures and tables must be kept to a minumum.
Guidelines exceeding 8 000 words will only be considered for publication as a supplement to the SAMJ*; the costs of which must be covered by sponsorship or advertising. The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.*

MANUSCRIPT PREPARATION

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - **www.icmje.org**. Manuscripts must be provided in **UK English**.
Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age'. The same applies to ± and º, i.e. '35±6' and '19ºC'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...' Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

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ILLUSTRATIONS AND TABLES

If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
Tables may be embedded in the manuscript file or provided as **'supplementary files'**. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'. Figure legends: Fig. 1. 'Title...' All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable, but images must not be resized to increase resolution. TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft Powerpoint or Excel must be accompanied by the original workbook.

REFERENCES

Authors must verify references from original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists must be generated manually and **not** with the use of reference manager software. Citations should be inserted in the text as superscript numbers between square

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Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID). Authors are encouraged to use the DOI lookup service offered by **CrossRef**.

Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. [http://dx.doi.org/10.1000/hgjr.182] [PMID: 2764753]

Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101. *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: publisher name, year; pages. Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'. Unpublished observations and personal communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

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