A DESCRIPTIVE STUDY OF NON-MELANOMA SKIN CANCERS IN PATIENTS ATTENDING CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL AND HELEN JOSEPH HOSPITAL FROM JULY 2013 TO JUNE 2016.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Dermatology

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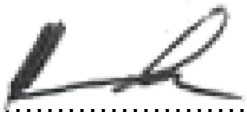
DECLARATION

I, Julia Ndeshihafela Ndakunda declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine in the branch of Dermatology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



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On the 8th day of May 2021 in Windhoek, Namibia

DEDICATION

To my God Almighty, for the source of wisdom and strength that he granted me to complete this project, and to my family, for their love, encouragement and endless support!

ABSTRACT

Introduction

Non-melanoma skin cancers (basal cell carcinomas and squamous cell carcinomas) are skin cancers derived from epidermal keratinocytes, and they are the most common tumours in humans in predominantly white populations. There are very few studies done on these cutaneous malignancies in South Africa.

Aim of study

The aim of this study was to describe the characteristics of non-melanoma skin cancers (NMSCs) in patients attending Charlotte Maxeke Johannesburg Academic Hospital and Helen Joseph Hospital.

Methods

A retrospective case review of histologically confirmed cases of non-melanoma skin cancers in patients seen at Charlotte Maxeke Johannesburg Academic Hospital and Helen Joseph Hospital between July 2013 and June 2016.

Results

A total of 356 cases of histologically confirmed non-melanoma skin cancers were reviewed. Of these, 74.7% were basal cell carcinomas and 25.3% were squamous cell carcinomas. Most non-melanoma skin cancers occurred in elderly male patients. The majority of non-melanoma skin cancers (74.4%) were observed on the sun exposed areas of the body. There was a statistically significant difference in the distribution (body site) of NMSCs in males and females ($p=0.018$ for basal cell carcinomas, and $p=0.014$ for squamous cell carcinomas).

Most basal cell carcinomas showed a mixed histological pattern (28.2%), whilst most squamous cell carcinomas (60%) were moderately differentiated invasive squamous cell carcinomas.

Nine percent (n=32) of patients had additional risk factors associated with development of non-melanoma skin cancers. HIV infection was associated with an increased risk of developing squamous cell carcinoma and not basal cell carcinoma.

Conclusion

Most non-melanoma skin cancers (NMSCs) occurred in elderly male patients, and were observed on the sun exposed areas of the body. Basal cell carcinomas (BCC) were the most common NMSC. There was a difference in the distribution (body site) of NMSCs in males and females. The predominant mixed histological pattern of BCC and the moderately differentiated SCC histological subtype in this study are associated with aggressive and intermediate clinical behavior, respectively. Meticulous recording and reporting of these skin cancers will aid in further research

of these cancers, which will result in proper allocation of healthcare resources required to diagnose, treat and prevent these highly preventable skin cancers.

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LIST OF ABBREVIATIONS

BCC	Basal cell carcinoma
DNA	Deoxyribonucleic acid
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
NMSC	Non-melanoma skin cancer
OCA	Oculocutaneous albinism
SCC	Squamous cell carcinoma
UV radiation	Ultraviolet radiation
XP	Xeroderma pigmentosum

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1. Introduction

The skin is the most common site of cancers in humans (Leiter and Garbe, 2008). The majority of skin cancers are made up of non-melanoma skin cancers (NMSC) (Leiter and Garbe, 2008). Non-melanoma skin cancers are skin cancers that are derived from epidermal keratinocytes, usually either basal cell carcinoma (BCC) or squamous cell carcinoma (SCC). Classically, nearly 80% of non-melanoma skin cancers are BCCs, with the remainder being SCCs (20%) (Cameron et al, 2019).

Sun exposure is the main cause of NMSCs. As a result, various programs to limit exposure of humans to UV radiation have been implemented lately, with the aim of reducing the incidence of these skin cancers (Olsen, Williams and Whiteman, 2014). Despite these efforts, the worldwide incidence of NMSCs has been increasing (Olsen, Williams and Whiteman, 2014), and is said to have reached epidemic proportions (Diepgan and Mahler, 2002). The high incidence of these skin cancers can be attributed to increased exposure to solar UV radiation, resulting from increased outdoor activities and professions, increased life expectancy, lack of protective clothing, inadequate use of sunscreens and climatic changes resulting in depletion of the ozone layer (Leiter and Garbe, 2008). The highest incidence of NMSCs is reported in Caucasian patients in Australia (Lomas, et al, 2012).

The increased incidence of NMSCs places a burden on healthcare resources. According to a report on Skin Cancer in Australia by the Australian Institute of Health and Welfare (AIHW), an astronomical amount of money is spent annually on skin

cancers, with approximately 10% of all health care spending on cancer in Australia allocated to the management of skin cancers in 2008-2009 (AIHW, 2016). Similarly, $8.4 billion was spent on the management of NMSCs in the United States (US) in 2007-2011 (Guy et al, 2015). Gordon et al (2016), also reported that skin cancer in South Africa is a growing public health issue, with approximately R 90 million was spent in 2015 to treat this condition. This massive spending on skin cancers puts pressure on the already strained healthcare resources (Gordon et al, 2016).

Although NMSCs are the most common skin cancer in humans, with an approximate incidence 20 times greater than that of melanoma skin cancers (Diepgan and Mahler, 2002), their exact incidence is unknown (Silverberg et al, 1990). Unlike other skin cancers, non-melanoma skin cancers are often overlooked and underreported, and often not recorded in cancer registries in most countries (Silverberg et al, 1990), including South Africa (Norval, Kellet and Wright, 2014). This is because, in contrast to melanoma skin cancers that are associated with a high mortality, NMSCs are associated with very low mortality.

BCCs are locally invasive and have low metastatic potential, whilst SCCs have a higher metastatic potential and therefore associated with a higher mortality compared to BCCs (Andrade et al, 2012).

NMSCs are reported to have accounted for approximately 1% of all cancer deaths in Australia 2016 (AIHW, 2016). Even though they are associated with very low mortality and have cure rates of nearly 95%, NMSCs can be associated with high

morbidity resulting from cosmetic disfigurement if not diagnosed and treated early (Trakelli et al,2007; Rezende et al, 2019).

1.2. Literature review

1.2.1. Incidence and prevalence of NMSCs

NMSCs are the most common type of cancer in predominantly white populations (Leiter and Garbe, 2008). The exact incidence and prevalence is not known, as NMSCs are often not registered in cancer registries (Firnhaber, 2012). Despite these inconsistencies, an astronomical increase in the incidence of these cancers has been reported by many longitudinal studies (Firnhaber, 2012). Green reported an annual average increase of up to 8% in NMSCs in white populations in Europe, the United States, Canada and Australia since the 1960s (Green, 1992). In the United States, NMSCs account for approximately 40% of all skin cancers (Diepgan and Mahler, 2002). In the United States alone, it has also been reported that over 3.5 million cases of BCCs and SCCs are seen every year (Rogers et al, 2010) Additionally, it has been stated that approximately 20% of Americans will likely develop skin cancers during their lifetime (Rigel, Friedman and Kopf, 1996). Similarly, high incidences of NMSCs have also been reported in Germany. In a recent article by Kraywinkel, Wolf and Katalanic (2012), it is stated that more than 200 000 cases of NMSCs are seen every year, making these cancers the most common malignancy in Germany.

The highest incidence of NMSCs in the world has however been reported in Australia (Lomas, Leonardi-Bee and Bath-Hextal, 2012), with incidence rates of 2% per year reported for NMSCs in some parts of Australia (Olsen et al, 2014). According to the 2016 AIHW report, approximately 70% of Australians will be diagnosed with cutaneous malignancy by the time they are 70 years (AIHW, 2016). Cutaneous malignancies are thus considered as a burden to the healthcare system in Australia (AIHW, 2016).

In contrast to Caucasians, skin cancers particularly NMSCs are reported to be less common in blacks, Hispanics and Asians (Gloster and Neil, 2006). In the United States, NMSCs are said to account for approximately 2- 4% of all neoplasms in these population groups (Gloster and Neil, 2006).Even though they are less common in these population groups, studies done in Japan demonstrated an increase in incidence of NMSCs in Asian populations (Seo et al 1998, Moon et al 1998). Similarly, the increase in incidence of NMSCs has also been reported in Singapore (Koh et al, 2003). Increased incidences have also been reported in South American countries such as Brazil (Andrade et al, 2012)

There are few studies done on the epidemiology of skin cancers in African countries including South Africa (Norval, Kellet and Wright, 2014). Black individuals predominate in most African countries. Analogous to studies done in the United States that showed that NMSCs are less frequent in black individuals, similar studies done in African countries such as Tanzania and Nigeria revealed similar findings (Amir, Mbonde and Kitinya,1992, Mandong et al 2000). South Africa’s population is,

however, more diverse. According to the 2001 census, South African population comprised of 79.4% blacks, 9.2% whites, 8.8% coloureds and 2.6% Asians (Norval, Kellet and Wright, 2014). The close proximity of South Africa to the equator, with resultant high level of solar UV radiation all year round, predisposes South Africans at an increased risk of developing non-melanoma skin cancers (Norval Kellet and Wright, 2014). Wright et al (2014), stated that skin cancer in South Africa, especially in whites is amongst the highest in the world (Wright et al, 2014)

Although NMSCs are less common in Blacks, Hispanics and Asians, they are reported to be associated with a greater morbidity and mortality as most often, their diagnosis is delayed due to patients' lack of awareness and limited access to health care facilities (Agbai et al, 2014).

1.2.2. Pathogenesis and risk factors

As shown in table 1.1, there are various risk factors associated with development of NMSCs.

According to Leiter and Garbe (2008) and Wikonkal and Brash (1999), the majority of these skin cancers occur as a result of UV light exposure, which, when combined with a number of other risk factors leads to cell damage, and failure to repair DNA, leading to the accumulation of DNA mutations and malignant transformation.

Table 1.1: Risk factors for non-melanoma skin cancers (Adapted from Trakelli et al, 2007)	
Endogenous	**Exogenous**
Age	Ultraviolet radiation (sunlight and artificial tanning lamps)
Genetic predisposition (skin type)	
Previous history of a NMSC	PUVA therapy
Genetic diseases (Xeroderma pigmentosa, Gorlin's syndrome, albinism)	Ionizing radiation
	Chemical carcinogens (arsenic, tobacco)
	Infections (HPV, HIV infections)
	Scarring
	Iatrogenic (immunosuppression in organ transplant patients)
	Proximity to the equator, high altitude

Table 1.1 shows the risk factors associated with development of non-melanoma skin cancers

1.2.2.1 Ultraviolet (UV) radiation

- **Sun Exposure**

Exposure to UV radiation is the main cause of non-melanoma skin cancers (Diepgan and Mahler, 2002). The carcinogenicity of UV radiation from the sun has been reaffirmed by the International Agency for Research on Cancer in 2009 (Ghissassi et al, 2009). UV radiation has been proven to cause DNA damage, which results in the development of cutaneous malignancies (Wikonkal and Brash, 1999). In addition, de Villiers (1998) reported that UV radiation induces a state of immunosuppression that encourages development of skin cancers. Furthermore, UV radiation encourages persistent infection with human papilloma virus (HPV), which is implicated in the

development of NMSCs, particularly in immunosuppressed patients (de Villiers, 1998).

Chronic, cumulative exposure to UV radiation has been implicated in the development of SCCs, whilst intermittent and cumulative sun exposure has been linked to the development of BCCs (English et al 1998, Kricker, Armstrong and English, 1994, Kricker et al, 1995). Increased exposure to UV radiation, as seen in outdoor occupations and during recreational activities, accompanied by lack of sunscreen use and other sun protective measures, results in an increased risk of developing NMSCs. (Andrade et al, 2012). The majority of these cancers, particularly basal cell carcinomas, occur in body sites that are constantly exposed to the sun, such as head, neck, arms and dorsal hands (Diepgan and Mahler, 2002). Conversely, NMSCs are infrequently found on areas of the body that are rarely exposed to the sun such as the buttocks in both men and women and the scalp in women (Rigel, 2008). The role of sunlight in the development of NMSCs is further affirmed by the occurrence of these cancers on sun exposed areas of the body (Madan, Lear and Szeimies, 2010).

With the exception of BCCs, sunlight does not appear to be an important aetiological factor in the development of NMSCs in darkly pigmented individuals, especially Blacks. As observed in Caucasians, BCCs in black patients occur on sun exposed areas, whilst SCCs occur on non- sun exposed areas and on sites of preexisting trauma such as burn wounds or chronic wounds (Diepgan and Mahler, 2002, Halder and Bridgeman-Shah, 1988).

The incidence rates of NMSCs is determined by the geographic location and coordinates of a region. According to a study done by Staples, Marks and Giles (1998), the highest rates of NMSCs have been reported from Australia and New Zealand. This geographic variation in the incidence of NMSCs can be attributed to different levels of solar UV radiation, further affirming the relationship between exposure to UV radiation and development of NMSCs. (Madan, Lear and Szeimies, 2010). Madan, Lear and Szeimies (2010) further states that the incidence of NMSCs is directly proportional to their closeness to the equator, as the ozone layer is thinner at these low latitudes and the distance traversed by UVB in these region is short compared to areas located at high latitudes. Similarly, the higher the altitude of a geographic area, the greater the risk of developing NMSCs (Andrade et al, 2012). Because of its proximity to the equator, South Africa has a high level of solar UV radiation, placing South Africans, particularly fair skinned individuals at an increased risk of developing skin cancers (Wright, 2012) .This level of risk is described to be amongst the highest in the world (Human and Bajic, 2002).

- **Tanning devices**

Indoor tanning devices emit artificially produced UV radiation, and are reported to emit up to five times the UV radiation of midday summer sun (Walter et al, 1990). The use of tanning devices has been associated with an increased risk of developing NMSCs. In 2009, UV-emitting devices were classified together with solar radiation as carcinogens by the International Agency for Research on Cancer (Ghissassi et al, 2009).

Indoor tanning has become a popular source of UV radiation, especially in the United States and European countries. These devices are normally utilized by young adults, particularly females. It has been reported that the increased use of indoor tanning devices in these countries has resulted in a proportional increase in non-melanoma skin cancers, especially in young females (Ferruci et al, 2012). Ferruci et al further reported that people exposed to indoor tanning devices have a nearly 70% increased risk of developing BCC at an early age. The risk is said to be directly proportional to the number of years an individual is regularly exposed to indoor tanning devices and overall burns from these. As opposed to BCCs that develop in sun exposed areas, the BCCs in people exposed to indoor tanning devices tend to develop on the trunk and extremities (Ferruci et al, 2012).

There is paucity of data available with regards to use of tanning devices and subsequent development of skin cancers in Asian and African countries, including South Africa.

1.2.2.2. Race

The risk of NMSCs is higher in patients with Fitzpatrick's skin type I and II, i.e.fair-skinned, blue eyed individuals with red or blond hair who tan poorly, sunburn easily and freckle when exposed to the sun, than in patients with darker skin phenotypes i.e Blacks, Asians and Hispanics (Gilchrest et al, 1999; Diepgan and Mahler, 2002).The high incidence of these cancers in Caucasians is attributed to low epidermal melanin. Epidermal melanin protects individuals from the harmful effects of solar radiation. In contrast, dark skinned individuals have high epidermal

melanocyte activity, which only allows transmission of approximately 10% of UVB compared to approximately 25% of transmission of UVB in fair skinned individuals. Moreover, dark skinned individuals have been documented to have an intrinsic sun protection factor of 13.4, which is four times higher than in Caucasians. This inherent photoprotection thus results in a low incidence of NMSCs in individuals with a darker skin phenotype (Halder and Bridgeman-Shah, 1995, Scotto, Fears and Fraumeni, 1983, Montagna, Prota and Kenney, 1993).

BCC is more common than SCC in populations with a predominant Caucasian population. A study done by Gallagher et al (1995), noted that individuals with Fitzpatrick skin phenotype I and II are more likely to develop BCCs than those with darker skin phenotypes. In darkly pigmented populations, however, SCC is more common than BCC (Gloster and Neil, 2006; York et al, 2017). There is, however, limited data in the literature with regards to NMSCs in darkly pigmented individuals, as most studies on NMSCs are done in predominantly white populations (Gloster and Neil, 2006). An analysis of the Singapore Cancer Registry between 1968 and 1997 showed a higher incidence of skin cancers in fair skinned Chinese compared to their darker counterparts who were of Indian or Malay descent, further confirming the low incidence of NMSCs in darkly pigmented individuals (Koh et al, 2003). Studies done in the United States also reveal that NMSCs are less common in black individuals (Gloster and Neil, 2006). Studies done in Africa revealed similar findings (Amir, 1992; Mandong et al, 2000; Ochika et al, 2004). Moreover, the higher incidence of NMSCs, particularly BCCs, in fairer skinned albinos further supports the increased incidence of NMSCs in light skinned individuals compared to their dark skinned counterparts (Amir, 1992; Mandong et al, 2000; Ochika et al, 2004, Kromberg et al, 1989; Kiprono, Chaula and Beltraminelli, 2014).

An analysis of the South African Cancer Registry done between 2000 and 2004 also revealed a lower incidence of NMSCs in Blacks, Coloureds, and Asians compared to their white counterparts, further confirming the protective effects of higher quantities of epidermal melanin against solar UV radiation and subsequent development of NMSCs in darker skinned individuals (Norval, Kellet and Wright, 2014).

1.2.2.3. Age

NMSC is primarily a disease of the elderly. According to the 2016 Skin Cancer Australia report, NMSCs were commonly seen in elderly individuals after the 8th decade of life and less so in young people below age 40 years (AIHW, 2016). In another report by Diffey and Langtry (2005), NMSCs in individuals above 60 years accounted for more 80% of all NMSCs, further affirming the occurrence of these cancers predominantly in elderly people. In a report by Holme, Malinovszky and Roberts (1998), it is also stated that the incidence of SCC in individuals over the age of 75 was 7 times higher than that of BCC. It is further stated that, compared to BCC, the incidence of SCC increases astronomically with age than that of BCC (Holme, Malinovszky and Roberts, 2000).

Studies done in Africa, with predominantly Black populations, however, revealed that NMSCs occur in younger patients, compared to their Caucasian counterparts. A study from Nigeria showed an average age of approximately 45 years for BCCs, and 50 years for SCCs in a retrospective study on skin cancers between 1982 to 2007 (Forae and Olu-Eddo,2013). In Northern Cape, South Africa York et al reported a slightly older age group in a retrospective study done between 2008 and 2012, with BCCs reported to occur more frequently in the age group 60-69, whilst SCC

occurred more commonly between 50-59 years of age (York et al, 2017), slightly lower than that reported in western countries.

Although NMSCs are most commonly seen in elderly people, the incidence of NMSCs is also reported to be increasing in younger individuals. This is mostly due to the use of tanning devices, which are commonly used by young individuals as well as excessive recreational exposure to solar UV radiation (Lin, Eder and Weinmann, 2011, Ferruci et al, 2012).

1.2.2.4. Sex

NMSCs are classically more common in males than in females. In the Skin Cancer in Australia report, the incidence rate of BCCs in males increased by approximately 40% from 1985 to 2002 compared to an increase of 25% seen in females over the same period (AIHW, 2016). Similarly in South Africa, NMSCs were reported to occur twice as commonly in males compared to females (Norval, Kellet and Wright, 2014). This is attributed to greater exposure to solar UV radiation in males compared to females, as they are more likely to have outdoor professions, and are less likely to use sunscreens and protective clothing during recreational exposure to UV light (Ghallagher et al, 1995, Norval, Kellet and Wright, 2014, Abbas and Kalia, 2016). This difference, however, is only seen in elderly individuals and not in younger individuals with NMSCs (Abbas and Kalia, 2016). Contrary to this trend, Ferruci et al (2012) reported an increased incidence of NMSCs in young female patients due to exposure to UV radiation from indoor tanning devices.

1.2.2.5. Other risk factors

- **Family history of NMSC**

Individuals with a family history of NMSC are said to be at an increased risk of developing NMSC than individuals with no known family history of NMSCs (Herity et al, 1989).

- **Previous history of NMSC**

Individuals with a previous history of a NMSCs are at increased risk of developing another NMSCs. According to Madan, Lear and Szeimies (2010), individuals diagnosed with a NMSCs for the first time have a 50% chance of developing a subsequent NMSC within the first five years of being diagnosed with a NMSC. The appearance of the first BCC on the trunk, male sex, occurrence of BCC after the 6th decade of life and a superficial histology subtype has been associated with a high risk of developing recurrent multiple BCCs (Marcil and Stern, 2000).

- **Genetic disorders**

NMSCs may be associated with some rare genodermatoses.

As tabulated in table 1.2, BCCs have been associated with genodermatoses such as basal cell naevus syndrome (Gorlin's syndrome), xeroderma pigmentosum, Rombo's syndrome, Muir-Torre syndrome, Rothmund-Thomson syndrome and oculocutaneous albinism (OCA), to mention a few. Patients with Gorlin's syndrome

have a defect in the Hedgehog signaling pathway which results in development of multiple BCCs at an early age as well as developmental defects (Cameron et al, 2019). Individuals with xeroderma pigmentosum have an inability to repair defective genes, resulting in accumulation of mutated genes. This results in a 10 000 fold increased risk of developing malignancies, including BCCs at an early age (Jaju et al, 2016).

Table 1.2: Genetic disorders associated with increased risk of developing BCC (Adapted from Cameron et al, 2019)

Syndrome	**Gene**	**Function**
Basal cell naevus syndrome	PTCH 1, PTHCH 2, SUFU	Hedgehog signaling pathway
Xeroderma pigmentosum	XPA-XPG, XPC	Nucleotide excision repair
Oculocutaneous albinism	TYR, TYRP1, P, MATP	Production of melanin
Muir-Torre syndrome	MLH1, MSH2,MSH6,PMS2	Mismatch repair
Rothmund-Thomson syndrome	RECQL4 and C16Orf57	Chromosomal stability, telomere maintenance, trafficking

Table 1.2. Genetic disorders associated with increased risk of developing BCCs

Similarly, genetic syndromes such as epidermodysplasia verruciformis (EDV), xeroderma pigmentosum (XP), OCA and some forms of epidermolysis bullosa are associated with an increased risk of developing SCCs, especially at an early age (Madan, Lear and Szeimies, 2010). Patients with EDV have a genetic mutation in the EVER1/2 genes, making them susceptible to HPV infections and subsequent development of NMSCs, particularly SCCs in up to 10% of individuals (Burger and Itin, 2014, de Jong et al, 2018; Gul et al, 2007). Individuals with OCA have a genetic

defect that results in the impaired biosynthesis of melanin. The risk of developing SCCs is significantly higher in these patients compared to the general population. In sub- Saharan Africa, the risk has been reported to be 1000-fold higher compared to the normal population (Lekalakala et al, 2015).

- **Infections**

Infections with HIV and HPV predispose individuals to develop NMSCs, especially SCCs.

In a study done by Silverberg et al, HIV positive subjects were reported to have up to twice the incidence of SSC compared to the normal population. The risk of developing BCC in HIV positive individuals, however, was found to be similar to that of HIV negative individuals, as the incidence for BCCs was reported to be the same for HIV positive and HIV negative individuals (Silverberg et al. 2013), further affirming that immunodeficiency increases the risk of developing SCCs and not BCCs (Silverberg et al, 2013). The risk of developing SCCs in these patients is reported to be related to the CD4 count and viral load: individuals with low CD4 counts and high viral loads are more likely to develop SCCs compared to individuals with high CD4 counts and low viral loads (Asgari et al, 2017). Zhao, Shu and Wang (2015) also reported in a recent study an increased risk of developing NMSCs in HIV positive individuals. This risk is said to decrease with initiation of ARV mediation (Zhao,Shu and Wang, 2015). South Africa is reported to have one of the highest incidences of HIV infections in the world, and thus an expected increased risk of developing SCCs in these individuals (UNAIDS, 2006).

HPV infection as a carcinogenic cofactor has been well documented in the development of anogenital cancers, particularly in immunosuppressed individuals, Carcinogenic HPVs have been isolated in most cervical cancer biopsies (zur Hausen, 2002). HPV infections, together with exposure to UV radiation, have also been associated with an increased risk of developing NMSCs, particularly SCCs (Hasche et al, 2017). This has been observed in immunosuppressed patients and patients with genetic disorders including EDV and xeroderma pigmentosum (Connoly et al, 2014). In contrast to anogenital cancers, HPV DNA is not commonly isolated from biopsies of cutaneous NMSCs, as viral DNA is often lost during the process of carcinogenesis (Hasche et al, 2017).

- **Immunosuppression**

Immunosuppression increases the risk of developing NMSCs, especially in organ transplant patients (Marzuka and Book, 2015). Marzuka and Book (2015) also stated that, compared to the general population, transplant patients are 250 times more likely to develop SCCs. NMSC has been reported as the commonest cancer observed in transplant patients, with incidence rates of SCCs reported to be 100 times greater than in normal individuals (Rodriguez-Acosta et al, 2015).

- **Miscellaneous risk factors**

The risk of developing NMSCs is increased in individuals who are exposed to chemical carcinogens such as tobacco, psolarens, and arsenic (Diepgan and Mahler 2002). SCCs have also been reported to develop in areas of trauma, such as burn wounds, scars and ulcers, especially in black individuals (Diepgan and Mahler, 2002). Chronic exposure to ionizing radiation also predisposes individuals to develop NMSCs (Azizova et al, 2018).

1.2.3. Clinical presentation

1.2.3.1. Basal Cell Carcinoma

Classically, BCC presents as nodular basal cell carcinoma - an enlarging, non-healing, transluscent, nodule with telangiectasia and most often with rolled edges, which in most cases will be ulcerated and may bleed on contact. It may be pigmented, especially in dark skinned individuals. Superficial BCC commonly presents as a scaly erythematous plaque, whilst morpheic BCC appears as an atrophic, scar like plaque (Rubin, Chen and Ratner, 2005, Cameron et al, 2019). Other clinical presentations include: fibroepithelial, which presents as a sessile nodule on the trunk; micronodular, which appears as a thin erythematous plaque; as well as basosquamous, and infiltrative type (Cameron et al, 2019).

BCCs typically develop on sun exposed areas. Although they can occur on any part of the body, the majority of cases are found in the head and neck region (80%). The remainder are found on the trunk (15%) and on the limbs. Any suspicious lesion

occurring on sun exposed areas needs to be biopsied to confirm the diagnosis of BCC and institute curative treatment (Rubin, Chen and Ratner, 2005).

1.2.3.2. Squamous Cell Carcinoma

SCC commonly presents as an enlarging, non-healing ulcerated nodule on sun exposed areas of elderly patients (Rinker et al, 2001, Alam and Ratner, 2001). They can be preceded by actinic keratoses, which are hyperkeratotic papules or plaques commonly seen on sun exposed areas of the body, or by Bowen's disease (Alam and Ratner, 2001). The risk of progression from actinic keratosis to SCC is reported to be approximately 10% over a 10 year period (Madan, Lear and Szeimies, 2010).

In contrast to UV induced SCCs that are commonly seen on the sun exposed areas, HPV induced SCC presents as an enlarging verrucous lesion on the anogenital area or periungual area (Moy et al, 1989).

1.2.4. Histologic subtypes

Classifying NMSCs is important, as the histologic subtype determines the clinical behavior of NMSCs.

1.2.4.1. Basal Cell Carcinoma

A study analyzing histologic patterns in 1039 consecutive cases of BCC by Sexton, Jones and Maloney (1990), as shown in table 1.3, identified 5 major histologic patterns: Nodular (21%), Superficial (17%), Micronodular (15%), Infiltrative (7%) and Morpheic (1%). The majority of cases had a mixed pattern (38.5%). Basosquamous, keratotic, clear cell, and basal cell carcinoma with matrical differentiation were described as uncommon BCC histologic patterns. Sexton, Jones and Maloney (1990) further reported a high incidence of positive tumour margins in micronodular, infiltrative and morpheic BCC, and in mixed patterns with combinations of nodular, micronodular and infiltrative histologic subtypes. Similarly, these histologic patterns are also associated with aggressive clinical behavior (Batra and Kelly, 2002). This is in contrast to nodular and superficial BCC that can be fully removed by a simple surgical excision in more than 90% of cases, and associated with less aggressive clinical behavior (Sexton, Jones and Maloney, 1990, Batra and Kelly, 2002).

Table 1.3: Major histologic pattern in the study on consecutive cases of BCC (Sexton, Jones and Kelly, 1990)

Histologic pattern	**Percentage (%)**
Mixed pattern	38.5
Nodular	21
Superficial	17
Micronodular	15
Infiltrative	7
Morpheic	1

Table 1.3 shows the major histologic pattern of BCCs

1.2.4.2. Squamous Cell Carcinoma

There are different histological subtypes of SCC that are associated with various degrees of clinical behavior, risk of metastasis and recurrence (Lohman and Solomon, 2001).

The majority of invasive SCCs fall under the conventional histologic subtype (Lohman and Solomon, 2001). This histologic subtype is further subdivided into three histologic grades, based on the degree of differentiation (Yanofsky, Mercer and Phelps, 2010). Well differentiated SCCs have a low degree of nuclear atypia, greater keratinization and are associated with less aggressive clinical behavior. In contrast, poorly differentiated SCCs have a high degree of nuclear atypia, reduced keratin production and are associated with aggressive clinical behavior. Moderately differentiated SCCs have histologic features of both poorly and well differentiated SCC and are therefore associated with intermediate clinical behaviour (Yanofsky, Mercer and Phelps, 2010).

Other histologic variants of SCC described in literature include: spindle cell SCC, a rare variant that is seen areas of trauma; Acantholytic SCC, which is commonly seen in the head and neck region of elderly patients post radiotherapy; clear cell SCC; spindle cell SCC; and SCCs with single cell infiltrates (Cassarino, DeRienzo and Barr, 2006, Paolino et al, 2017).

1.2.5. Prevention of NMSCs

Exposure to UV radiation, both occupational and recreational, as well as from indoor tanning devices, has been associated with an increased risk of developing NMSCs. This risk is found to be high amongst men, Caucasians of non-Hispanic origin, young adults and well off individuals, as they are exposed to occupational and recreational UV radiation, and tend not to use sunscreens and personal protective clothing to protect them from the carcinogenic effects of UV radiation (Buller et al, 2011). As described in literature, development of SCCs is associated with chronic exposure to UVR, whilst that of BCC is believed to occur as a result of intense, intermittent exposure to UV radiation during childhood (English et al, 1998; Kricker, Armstrong and English, 1994; Kricker et al, 1995).

Reducing both recreational and occupational sun exposure through behavioral changes such as avoiding sun exposure to midday sun, use of personal protective clothing such as long sleeved shirts, hats and sunglasses, avoidance of tanning beds as well as application of sunscreens to sun exposed areas therefore seems to be the main strategy in reducing the risk of developing NMSCs (Marzuka and Book, 2015).

Prophylactic use of sunscreens, however, has only been shown to significantly reduce the risk of developing SCCs and not that of BCCs (Van der Pols et al, 2006). In a randomized control trial conducted over a period of 8 years by Van der Pols et al, a 40% reduction in the incidence of SCCs was seen in individuals who applied sunscreen on sun exposed areas on a regular basis, compared to the control group

(Van der Pols et al, 2006). In contrast, there was no significant decrease in the incidence of BCC in subjects applying sunscreens on a regular basis, compared to the control group (Van der Pols et al, 2006).

Regular use of sunscreens was also found to reduce the risk of developing SCC in a prospective study in organ transplant patients in a study by Ulrich et al, and not that of BCC (Ulrich et al, 2009).

Regular use of sunscreen during childhood and adolescence could have a theoretical benefit in reducing the risk of developing BCC, as these skin cancers have been associated with intermittent, intense sun exposure during childhood (Gallagher et al, 1995). There is, however, paucity of studies done on the use of sunscreens in adolescents and teenagers and subsequent development of skin cancers during adulthood (Gallagher et al, 1995).

Although there is clear evidence that regular use of sunscreens and sun protective measures reduces the incidence of NMSCs, a study done in the US revealed that the majority of individuals do not use sunscreens, nor do they practice sun protective behaviour (Buller et al, 2011). In this study, only 30% of adults, most commonly older adults and women, applied sunscreen on a regular basis, avoided midday sun exposure and wore protective clothing. An overwhelming 70% of adolescents also reported recent sunburn, and young females reported the use of indoor tanning devices on a regular basis (Buller et al, 2011).

There is paucity of literature in the use of sunscreens and other sun protective measures in South Africa. Lund et al reported inadequate use of sunscreens and protective clothing in school children with albinism, which predisposes them to develop NMSCs (Lund and Gaigher, 2002).

In order to reduce the incidence of NMSCs, regular use of sunscreen, both during early childhood and adulthood, in males and females, as well as in individuals with both fair and dark skin phenotypes, should be encouraged , and supplemented with other preventive measures, as sunscreens do not provide absolute protection against UV radiation (Kutting and Drexler, 2010).

In addition to regular use of sunscreens and other preventative measures, public awareness campaigns on the importance of early detection and treatment of NMSCs as well as education of healthcare workers on early detection and treatment of these skin cancers should also be encouraged (Diepgan and Mahler, 2002).

1.2.6. Treatment

There are several treatment modalities available for the treatment of NMSCs, which may include surgical treatments, destructive methods, medical treatment, radiotherapy as well as chemotherapy (Madan, Lear and Szeimies, 2010).

Various factors influence the choice of treatment of NMSC, which may include: the clinical type; histological type of NMSC; the location of the tumour; the size of the

tumor; underlying patient medical conditions; as well as access to various treatment modalities and skilled personnel (Madan, Lear and Szeimies, 2010).

According to the British Association of Dermatologists guidelines for the management of NMSCs and other literature, the primary aim of treatment for a primary, low risk NMSCs is complete surgical excision with predetermined margins or complete destruction of the tumour with resultant good cosmesis as a secondary aim (Thissen, Neumann and Schouten, 1999, Motley, Kersey and Lawrence, 2003; Telfer, Colver and Morton, 2008). For high risk NMSCs, Mohs micrographic surgery, which has a 5 year cure rate of 99%, has been recommended (Madan, Lear and Szeimies, 2010; Cameron et al, 2019).

Curettage and cautery is another surgical treatment modality that is recommended for low risk BCCs, and has a 5 year cure rate of approximately 92% (Rowe, Carroll, and Day, 1989). Cryosurgery is another treatment option, particularly for low risk NMSCs, especially BCCs. However, it is associated with a higher risk of recurrence (up to 40% at 2 year follow up) compared to other treatment modalities (Madan, Lear and Szeimies 2010).

For advanced or metastatic NMSCs, the recommended treatment modality is either radiotherapy or chemotherapy (Telfer, Colver and Morton, 2008, Madan, Lear and Szeimies 2010).

Medical treatment modalities for NMSCs are recommended for patients with low risk superficial BCCs, especially if other treatment options are contraindicated (Cameron et al, 2019). These include amongst others: topical 5- fluorouracil; topical imiquimod; topical retinoids and ingenol mebutate (Cameron et al, 2019). In addition, superficial BCCs can also be treated with intralesional injections with 5- fluorouracil, interferons, and bleomycin (Cameron et al, 2019). Photodynamic therapy (PDT) is an additional treatment option available for superficial BCCs. However, a recurrence rate of approximately 18% following PDT was recorded in one study after 12 months of follow up (Varma et al, 2001).

1.3. Aims and objectives

The aim of this study was to describe the characteristics of squamous cell carcinomas and basal cell carcinomas in patients attending Charlotte Maxeke Johannesburg Academic Hospital and Helen Joseph Hospital.

The objectives of this study were:

- To calculate the number and percentages of patients with basal cell carcinoma, squamous cell carcinoma and total non-melanoma skin cancers in the various sexes, age groups, tumour sites (head and neck, upper extremities, lower extremities, trunk or other sites), and racial groups.

- To compare the frequency of basal cell carcinoma in males and females according to the tumour sites (head and neck, upper extremities, lower extremities, trunk or other sites)
- To compare the frequency of squamous cell carcinoma in males and females according to the tumour sites (head and neck, upper extremities, lower extremities, trunk or other sites).

- To calculate the frequency of the different histologic subtypes of basal cell carcinomas (eg. superficial, nodular, cystic, etc).

- To calculate the frequency of the different histologic subtypes of squamous cell carcinomas (eg. well differentiated, poorly differentiated, etc).

- To asses other risk factors that contribute to the development of skin cancers (e.g. genetic factors, infections such as HPV and HIV, immunosuppression)

1.4. Justification for the study

There is paucity of data in literature on NMSCs in South Africa. This retrospective study on NMSCs in patients attending these two major referral hospitals in Gauteng will help determine the characteristics of these skin cancers in these hospitals.

This type of study has not been done in these two hospitals before. Knowing the characteristics of these skin cancers will help determine the morbidity associated

with these skin cancers, as well as the burden these cancers place on the health care resources. This in turn will help in the reallocation of health care resources, and implementation of skin cancer preventive strategies, such as: the use of sunscreens and protective clothing; sun exposure avoidance; as well as early treatment and detection of non-melanoma skin cancers.

CHAPTER 2: PATIENTS AND METHODS

2.1. Study design

This study was a retrospective case review of laboratory reports of histologically confirmed non-melanoma skin cancers (NMSCs) of patients attending Helen Joseph Hospital and Charlotte Maxeke Johannesburg Academic Hospital, whose skin biopsies were submitted to the National Health Laboratory Service Anatomic Pathology Department at Charlotte Maxeke Johannesburg Academic Hospital from 1st July 2013 to 30th June 2016.

2.2. Patients

2.2.1. Inclusion criteria

- All histologically confirmed non-melanoma skin cancers of patients attending Helen Joseph Hospital and Charlotte Maxeke Johannesburg Academic Hospital, whose skin biopsies were submitted to the National Health Laboratory Service Anatomic Pathology Department at Charlotte Maxeke Johannesburg Academic Hospital from 1st July 2013 to 30th June 2016.
- Histology reports of patients from Helen Joseph Hospital and Charlotte Maxeke Johannesburg Academic Hospital were included exclusively, as the National Health Laboratory Service Anatomic Pathology Department at Charlotte Maxeke Johannesburg Academic Hospital services many more hospitals in the Gauteng Province other than these two hospitals.

2.2.2. Exclusion criteria

- Laboratory records of histologically confirmed non-melanoma skin cancers outside the time period (July 2013 to June 2016).
- Malignant tumours of the skin other than squamous cell carcinoma and basal cell carcinoma.
- Histopathological opinions that are inconclusive.
- Skin biopsies showing squamous cell carcinoma in-situ.
- Multiple biopsies of the same patient.

2.3. Methods and data abstraction

The following data were extracted from the histology reports:

1. Demographic data
    - Age of patient with NMSC provided in the histology report
    - Sex
    - Race
2. The types of NMSCs were recorded either as BCC or SCC from the histology reports.
3. The site of skin cancer was recorded according to the location provided by the clinicians on the histology report. The sites were documented as:
    - Head and neck
    - Upper extremities
    - Lower extremities
    - Trunk
    - Other sites
    - Not specified

4. The histologic subtypes of NMSCs were recorded
    - BCC (eg. superficial, nodular, cystic, etc)
    - SCC (eg. well differentiated, poorly differentiated, etc)
5. Associated risk factors such as: genodermatoses (xeroderma pigmentosa, Gorlin's syndrome, oculocutaneous albinism), infections such as HPV and HIV, as well as iatrogenic immunosuppression due to organ transplantation were also captured and recorded.

2.4. Statistical methods

Data was captured on Microsoft Excel (Microsoft Corp), then imported to Stata software. Data was cleaned to check for missing variables. All data was analyzed using Stata 14 (StataCorp LP College Station, TX). Descriptive statistics on demographics and general characteristics of patients were collated. Chi square and Fischer's Exact Tests were performed to check for associations between pairs of categorical variables, and statistical significance was considered when $p<0.05$.

2.5. Limitations

This was a retrospective case review of laboratory reports of histologically confirmed NMSCs of patients attending Helen Joseph Hospital and Charlotte Maxeke Johannesburg Academic Hospital. This study might be an underestimate of NMSCs in this population group, as most NMSCs, especially BCCs are not biopsied and sent for histology, and not all individuals with NMSCs visit hospitals (Silverberg, Boring and Squires, 1990, Norval, Kellet and Wright, 2014)

As expected in a retrospective study, there was a lot of missing data, particularly the race/ ethnicity of the patients, which is crucial in this study of NMSCs, as well as the HIV status of most patients. However, despite these challenges, this study will provide valuable information on NMSCs that will be useful for further research and allocation of healthcare resources required to diagnose, treat and prevent these skin cancers.

2.6. Ethics approval

Ethics approval (clearance certificate number M170236) was obtained from Human Research Committee (Medical) of the University of the Witwatersrand.

CHAPTER 3: RESULTS

3.1. Introduction

The results of the data analysis of the study are presented in this chapter. This is then followed by the discussion and conclusion chapters.

The sections in this chapter will be presented according to the objectives of the study:

- Demographics and general characteristics of non-melanoma skin cancers (NMSCs).
- Distribution of BCC in males and females according to the tumour site.
- Distribution of SCC in males and females according to the tumour site.
- Histologic types of BCC.
- Histologic types of SCC.
- Other risk factors associated with development of NMSC.

3.2. Demographics and general characteristics of NMSCs diagnosed by the Department of Anatomical Pathology at Charlotte Maxeke Johannesburg Academic Hospital from 1st July 2013 to 30th July 2016.

Table 3.1. Demographic data and general characteristics of NMSC

Characteristic	Categories	BCC		SCC		NMSC (Total)	
		n	%	n	%	n	%
Sex	Male	160	60.1	60	66.7	220	61.8
	Female	106	39.9	30	33.3	136	38.2
Age (years)	≤ 20	1	0.4	1	1.1	2	0.6
	21-30	0	0.0	2	2.2	2	0.6
	31-40	9	3.4	7	7.8	16	4.5
	41-50	21	7.9	6	6.7	27	7.6
	51-60	47	17.7	11	12.2	58	16.3
	61-70	70	26.4	29	32.2	99	27.9
	71-80	87	32.8	26	28.9	113	31.8
	81-100	30	11.3	8	8.9	38	10.7
	Not specified	1	0.4	0	0.0	1	0.4
Tumour site	Head and neck	161	60.5	54	60.0	215	60.4
	Upper extremities	37	13.9	12	13.3	49	13.8
	Lower extremities	27	10.1	10	11.1	37	10.4
	Trunk	33	12.4	3	3.3	36	10.1
	Other sites	0	0.0	9	10.0	9	2.5
	Not specified	8	3.0	2	2.2	10	2.8
Race	Black	14	5.3	19	21.1	33	9.3
	Not specified	252	94.7	71	78.9	323	90.7

Table 3.1 shows a summary of the demographic data and general characteristics of non-melanoma skin cancers (NMSCs).

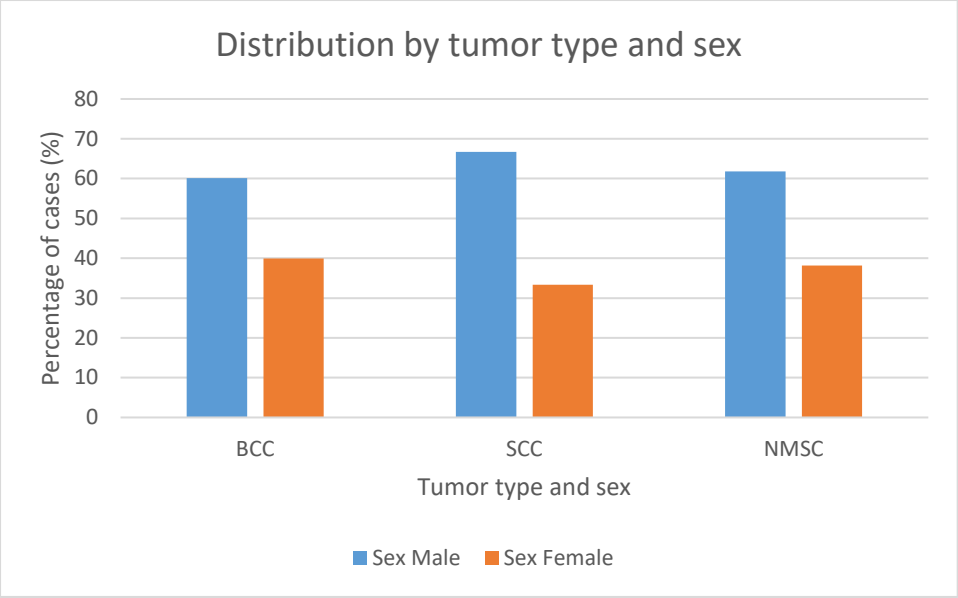

Figure 3.1: Distribution by tumour type and sex

A total number of 356 cases of NMSCs were diagnosed in patients attending Helen Joseph Hospital and Charlotte Maxeke Johannesburg Academic Hospital over the three-year period. Of these cases, 74.7% (n= 266) were BCCs and 25.3% (n =90) were SCCs.

Most non-melanoma skin cancers (NMSCs) were diagnosed in male patients (61.8%), and the remainder in females (38.2%). Of the 266 cases of BCCs diagnosed during this period, 60.1% (n=160) of patients were males, and the rest 39.9% (n=106) were females. Of the 90 cases of SCCs recorded, 66.7% (n =60) were males and 33.3% (n=30) were females. Distribution of NMSC by tumour type and sex is depicted graphically in figure 3.1.

The majority of these patients (70.4%) with NMSCs were above 60 years of age, and patients below 40 years of age accounted for only 5.7% (n=18) of patients of the total NMSCs. Similarly, most patients with BCCs (70.5%) were above 60 years of age, and only 3.8% (n=10) of individuals were below age 40 years. As in BCCs, a large proportion of the patients (70%) with SCCs were elderly patients above the age of 60 years and only one patient was under 20 years of age.

Most non-melanoma skin cancers were in the head and neck region as well as on the upper extremities (74.2%). The sites least affected by the NMSCs were the trunk, accounting for 10.1% of the cases, and the buttocks and genital areas (2.5%). Likewise, the majority of patients with BCCs (74.4%) had tumours located on sun exposed sites (head and neck region and upper extremities), whilst the lower extremity accounted for the least number of cases (10.1%). Similar to BCCs, the majority of SCCs (60%) were located on the head and neck area. The upper limbs were the second most affected area, accounting for 13.3% of the cases. As opposed to BCCs where 12.4% of the tumours were located on the trunk, only 3.3% (n=3) of SCCs were located on the trunk.

The race of most patients (90.7%) was not specified in the histology reports. In patients with SCC, 19 patients (21.1%) of patients had their race specified as Black, and only 14 (5.3%) patients with BCC had their race specified as Black.

3.3. Distribution of BCC tumour site by sex

Table 3.2. : Distribution of BCC tumour sites by sex (p=0.018)				
Tumour site	**Male**		**Female**	
	n	**%**	**n**	**%**
Head and neck	88	55.0	73	68.9
Upper extremities	26	16.3	11	10.4
Lower extremities	23	14.4	4	3.8
Trunk	19	11.8	14	13.2
Not specified	4	2.5	4	3.8
Total	160	100.0	106	100.0

Table 3. 2: shows the distribution of BCCs in males and females according to the tumour site.

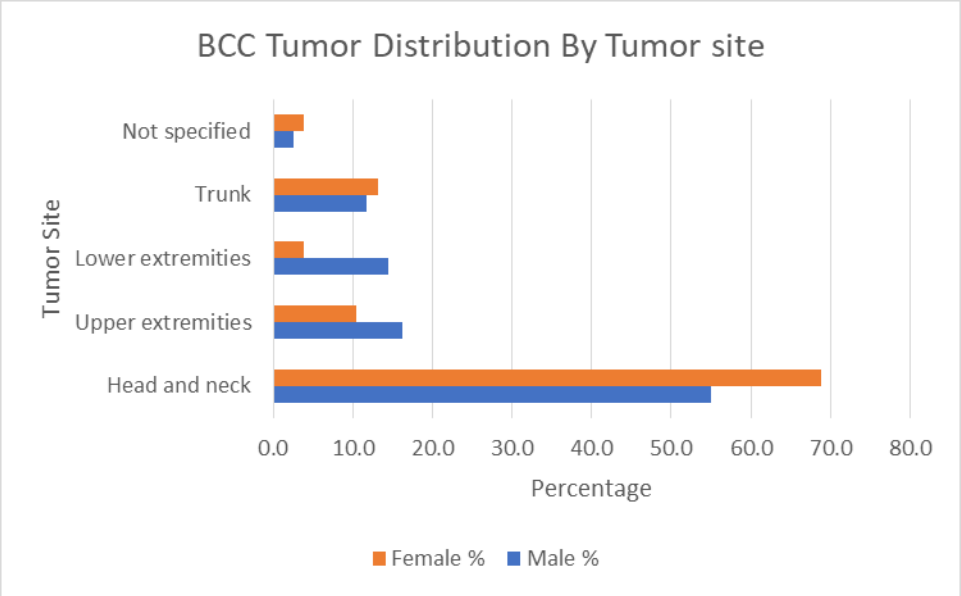

Figure 3.2. Distribution of BCC tumour site by sex

There was a statistically significant difference between the distributions (body site) of BCCs in males and the BCCs in females (p=0.018).

Of the 160 males diagnosed with BCCs, 88 patients (55.0%) had tumours located on the head and neck region. The upper extremities were the second most common site, with 16.3% (n =26) recorded. Twenty three patients (14.4%) had BCCs on the lower limbs, and 11.8% of BCCs were located on the trunk.

Similar to the location of BCCs in males, most female patients with BCCs had tumours located in the head and neck region (68.9%). As opposed to males, the trunk was the second most common location for BCCs in females, accounting for 13.2% of the cases. The site least affected by BCCs in females was the legs, with only four female patients reported to have had BCCs on the legs. Distribution of BCC tumour site by sex is depicted graphically in figure 3.2.

3.4. Distribution of SCC tumour site by sex

Table 3.3: Distribution of SCC tumour sites by sex (p=0.014)

Tumour site	Male		Female	
	n	%	n	%
Head and neck	42	70.0	12	40.0
Upper extremities	8	13.3	4	13.3
Lower extremities	4	6.7	6	20.0
Trunk	1	1.7	2	6.7
Other sites	3	5.0	6	20.0
Not specified	2	3.3	0	0.0
Total	60	100.0	30	100.0

Table 3.3 depicts the distribution of SCC in males and females according to tumour site.

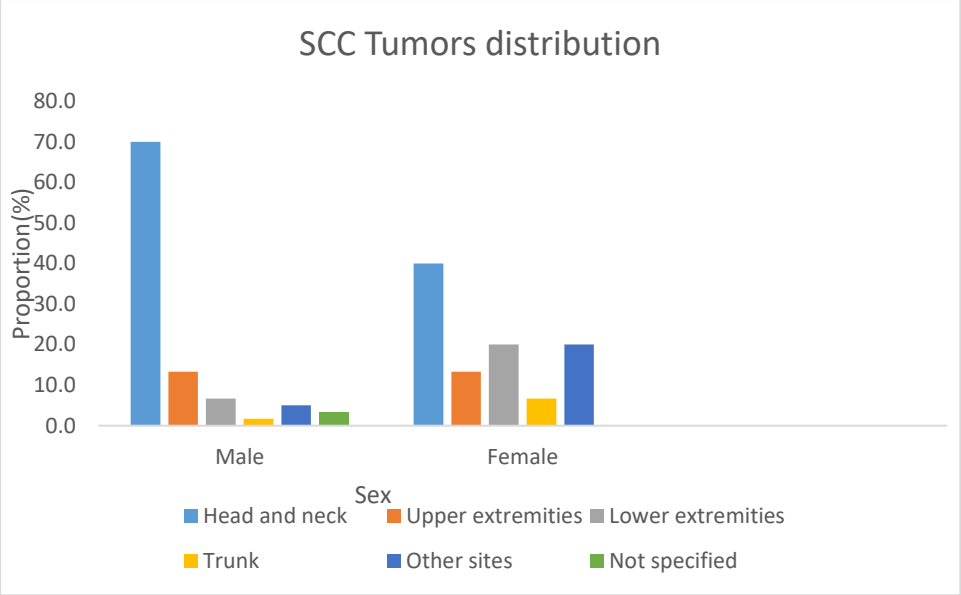

Figure 3.3 shows the graphical distribution of SCC tumour site by sex.

There was a statistically significant difference between males and females in the distribution (body site) of SCCs (p=0.014).

An overwhelming 70% (n=42) of male patients with SCC had tumours located on the head and neck region. The upper extremity was the second most common location of SCC in males, accounting for 13.3% of the cases. The rest of the SCCs in males were located on the trunk (1.7%) and on other sites such as the buttocks, fingers and genital area (5%).

Similarly, in females, the most common site of SCCs in this study was found to be the head and neck region (40%) followed by the upper extremities (13.3%). As opposed to males, a larger proportion of female patients (20%) had SCCs located on the lower limbs. A notable proportion of female patients (20%) also had SCC at other sites such as genital area and buttocks. Distribution of SCC tumour site by sex is shown graphically in figure 3.3.

3.5. Histologic subtypes of BCCs

Table 3.4.: Histologic subtypes of BCC		
Histologic type	**N**	**%**
Superficial	27	10.2
Nodular	44	16.5
Micronodular	9	3.4
Adenoid	7	2.6
Morpheic	19	7.1
Basosquamous	19	7.1
Mixed	75	28.2
Others	57	21.4
Not stated	9	3.4
Total	266	100.0

Table 3.4 and Figure 3.4 show the different histologic subtypes of BCCs.

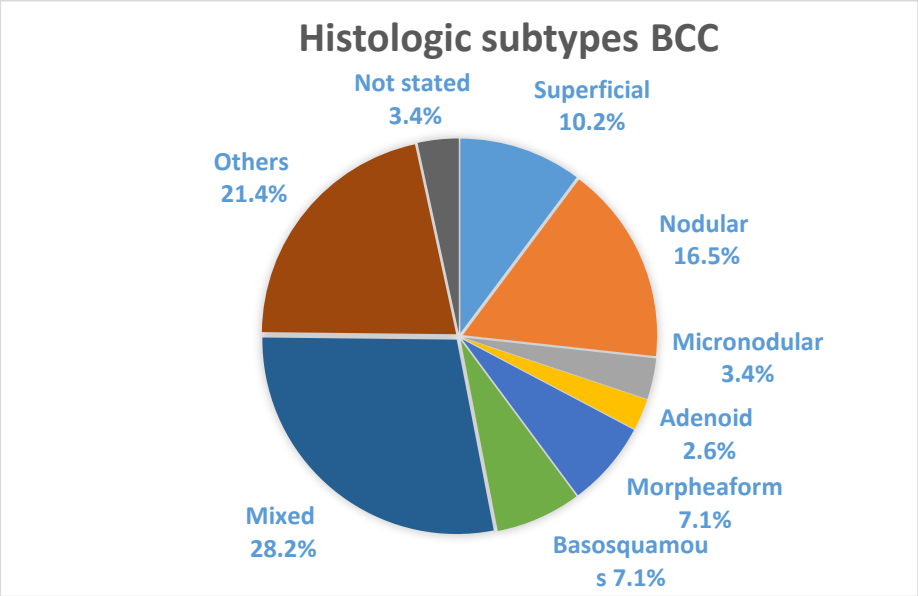

Figure 3.4. Histologic subtypes of BCCs.

The majority of the cases (28.2%), had a mixed histology, comprising different histologic subtypes of BCCs such as nodular and adenoid; nodular and micronodular; morpheic and superficial; and various other combinations.

Nodular BCC was the second most common histologic subtype observed in this study, accounting for 16.5% of the cases. This was followed by the superficial histologic subtype, seen in 10.2% of cases. The least common histologic subtypes were adenoid (2.6%) and micronodular BCC (3.4%)

Nine (3.4%) of the histology reports did not state the histologic subtypes of BCC.

The different histologic subtypes of BCC are depicted graphically in figure 3.4.

3.6. Histologic subtypes of SCC

Table 3.5: Histological subtypes of SCC		
Histologic type	**n**	**%**
Well differentiated	22	24.4
Moderately differentiated	53	58.9
Poorly differentiated	5	5.6
Acantholytic	4	4.4
Others	1	1.1
Not stated	5	5.6
Total	90	100.0

Table 3.5 and Figure 3.5 show a complete breakdown of the histological subtypes of SCC recorded in this study.

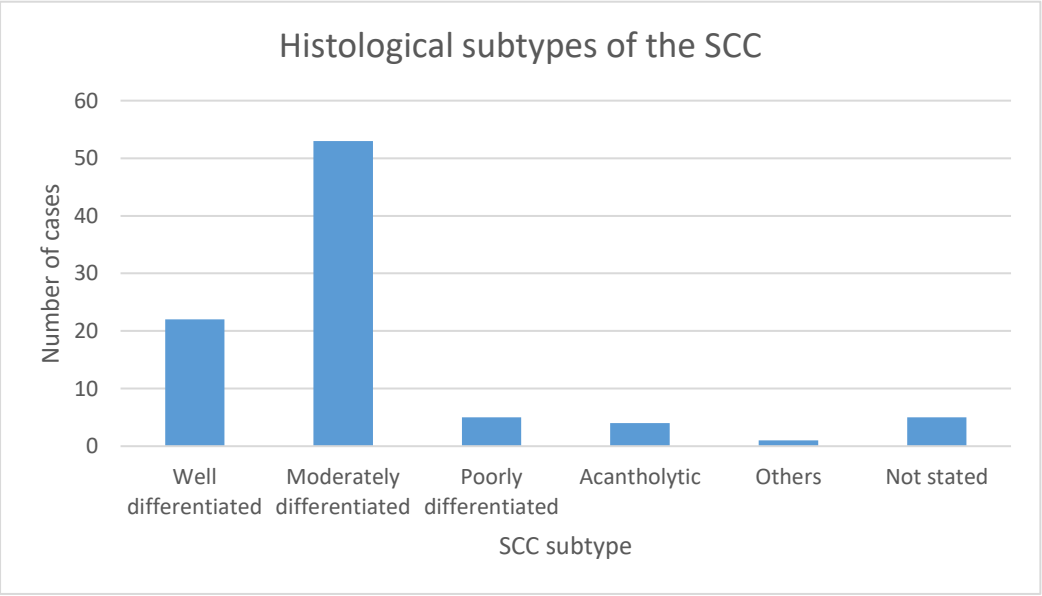

Figure 3.5. Histological subtypes of SCC

The majority of SCCs in this study were moderately differentiated (58.9%). This was followed by well differentiated SCC (24.4%).Poorly differentiated SCC accounted for 5.6% of all the histological subtypes.

Other histological subtypes of SCC recorded in this study were acantholytic (4.4%) and keratotic type (one histology report).

3.7. Other risk factors associated with development of NMSCs

Table 3.6. : Distribution of other risk factors by tumor type

Risk factor	**BCC**		**SCC**		**NMSC (Total)**	
	n	**%**	**n**	**%**	**n**	**%**
Xeroderma pigmentosus	1	0.4	1	1.1	2	0.6
Oculocutaneous albinism	11	4.1	2	2.2	13	3.7
EDV	1	0.4	2	2.2	3	0.8
HIV	0	0.0	3	3.3	3	0.8
Immunosuppresive agents	7	2.6	2	2.2	9	2.5
Other risk factors	1	0.4	1	1.1	2	0.6
Not specified	245	92.1	79	87.8	324	91.0

Table 3.6 shows the other risk factors associated with development of NMSCs.

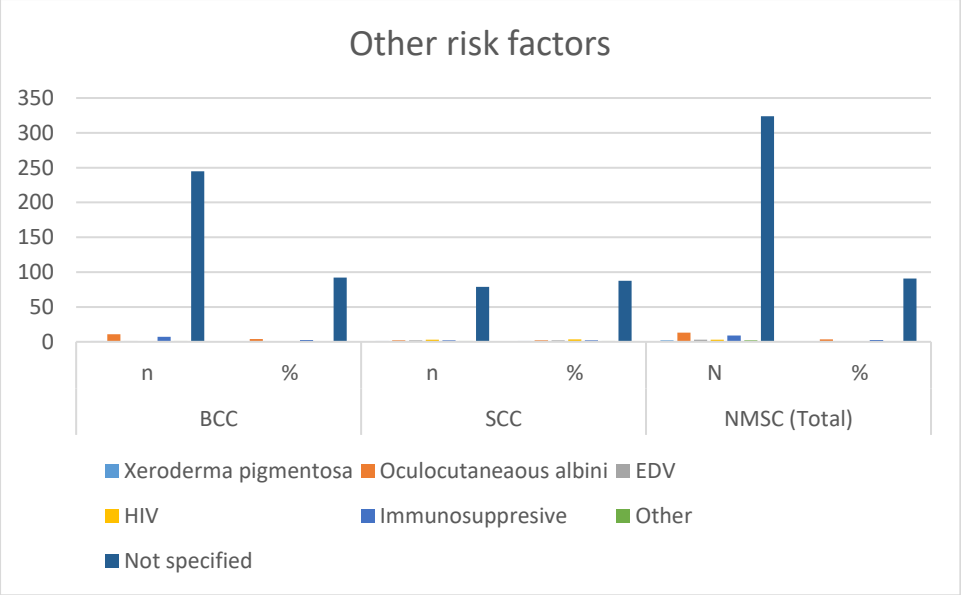

Figure 3.6. Other risk factors associated with NMSCs

Other risk factors associated with development of NMSCs are shown graphically in Figure 3.6.

Most of the patients with NMSC did not have a specified risk factor (n=324, 91%).

Thirteen patients (3.7%) with NMSCs had oculocutaneous albinism (OCA). Nine patients (2.5%) had undergone organ transplantation and were on immunosuppressive agents. Three patients had epidermodysplasia verruciformis (EDV), and two patients were diagnosed with xeroderma pigmentosum.

In patients with BCCs, 11 cases (4.1%) of oculocutaneous albinism (OCA) were recorded. Seven patients (2.6%) were on immunosuppressive agents following organ transplants. One patient had EDV, and there were no patients with HIV reported.

Only a few patients with SCCs were documented to have additional risk factors. Three patients were documented to have HIV and there were only two cases of OCA recorded. Other risk factors that were identified in patients with SCC were: EDV (n=2); immunosuppressive agents (n=2); and XP (n=1).

CHAPTER 4: DISCUSSION

4.1. Introduction

The findings of this study will be discussed in this chapter according to the study objectives, and will be compared with findings on non-melanoma skin cancers in the published literature. The discussion will then be followed by the conclusion and recommendations.

The aim of this retrospective study was to describe the characteristics of 356 histologically confirmed cases of NMSCs (BCCs and SCCs) in patients seen at Charlotte Maxeke Johannesburg Academic Hospital and Helen Joseph Hospital from July 2013 to June 2016.

4.2. Demographic data and general characteristics of NMSCs

Of the 356 cases of non-melanoma skin cancers (NMSCs) diagnosed in our patients, BCCs represented approximately three quarters of the cases (74.7%), whereas SCC, accounted for 25.3% of the cases. This higher prevalence ratio of BCC over SCC of approximately 3:1 is in keeping with other studies where BCC predominated over SCCs (ratio 4:1 to 2:1) in predominantly white populations (Cameron et al, 2019).

Although the race of these patients was not specified in most cases, the assumption is that most patients who were diagnosed with NMSCs in our study were

Caucasians. This assumption is supported based on the ratio of BCCs to SCCs seen in this study, commonly seen in predominantly white populations (Cameron et al, 2019).

Most non-melanoma skin cancers (NMSCs) were diagnosed in male patients (60.1%) compared to female patients (39.9%). This is in keeping with international and South African studies, where male sex was reported as predominant (Ghallagher et al, 1995; Norval, Kellet and Wright, 2014; Abbas and Kalia, 2016). The male sex predilection of NMSCs in our patients can be explained by excessive exposure to sunlight, as males are more likely to have outdoor occupations, as well as lack of protective clothing and sunscreen use compared to their female counterparts (Ghallagher et al, 1995; Norval, Kellet and Wright, 2014; Abbas and Kalia, 2016).

In our study, the majority of patients with NMSCs were elderly patients above 60 years of age (70.4%), and only a mere 5.7% (n=18) were below 40 years of age. Only two patients (0.6%) with NMSCs were below 20 years of age. As expected, this result demonstrates a higher prevelance of NMSCs in elderly patients as described in predominantly white populations in the international literature (Cameron et al, 2019; Diffey and Langtry, 2005, Holme, Malinovszky and Roberts, 2000). However, this age group is older compared to the findings in predominantly dark skinned populations and most African countries, including South Africa, where BCCs and SCCs occurred in younger patients (Samaila and Adewuyi, 2005, Forae and Olu-Eddo, 2013, York et al, 2017). Although the race of most patients was not provided

in the histology reports, the high prevalence of NMSCs in elderly patients in our patients could be due to the fact that most patients in our study might have been fair skinned individuals, who had chronic exposure to the harsh South African solar radiation spanning several decades (Wright et al, 2012, Diepgan and Mahler, 2002).The rarity of NMSCs observed in young patients in this study is also in keeping with international trends. The occurrence of BCCs and SCCs in these young patients could be attributed to the fact that these patients have other associated risk factors such as OCA, EDV, HIV and HPV infections (Cameron et al, 2019; York et al, 2017; Jaju et al, 2016, Lekalakala et al, 2015).

In keeping with international studies, most NMSCs (74.2%) in our patients were located on the head and neck regions as well as the upper extremities. Similarly, the majority of BCCs (74.4%) and SCCs (60%) were located in the head and neck region and upper extremities. The least affected sites were the non-sun exposed areas such as the trunk, buttock and genital areas (Andrade et al, 2012, Diepgan and Mahler, 2002, Madan, Lear and Szeimies, 2010). The higher number of NMSCs diagnosed on sun exposed areas of the body affirms the role of chronic exposure to ultraviolet radiation in the development of NMSCs (English et al, 1998, Kricker, Armstrong and English, 1994, Kricker et al, 1995). These findings are, however, not in keeping with reports from Africa and other predominantly Black populations, where most NMSCs, particularly SCCs occur on non-sun exposed areas of the body, particularly in chronic wounds and areas of trauma (Gloster and Neil, 2006, Samaila and Adewuyi, 2005; Ochicha et al, 2004, Diepgan and Mahler, 2002, Halder and Bang, 1988). Although the race of these patients was not specified in the histology report, it is assumed that majority of patients were fair skinned individuals as the

location of the NMSCs in this study mirrors that seen in predominantly white populations (Diepgan and Mahler, 2002; Halder and Bang, 1988).

Unfortunately, as previously stated, the race of most patients in this study was not specified (90.7%), except in 33 patients (9.3%) whose race was specified to be black because of the associated risk factors such as OCA, EDV and HIV and HPV infections. The assumption, however, is that the study group comprised largely of fair skinned individuals, as these two hospitals serves a significant number of fair skinned individuals. Moreover, the demographic data and characteristics of NMSCs seen in these patients fits a profile of NMSCs in predominant white populations described in literature.

4.3. Distribution of BCC in males and females according to the tumour site

There was a statistically significant difference between the distributions of BCCs in males and the BCCs in females in our study (p=0.018).

As expected, and in keeping with international and local findings, the majority of BCCS in both males and female patients (71.3% and 79.3% respectively) were located on the head and neck region as well as the upper extremities (sun exposed areas of the body), again emphasizing the association between these malignancies and sun exposure in both sexes (Norval, Kellet and Wright, 2014; Andrade et al, 2012; Diepgan and Mahler, 2002).

In the literature, more males than females have BCCs located on the trunk (Buettner et al, 1998). In our study, BCCs located on the trunk were more common in females (13.2%) than in males (11.8%). Although traditionally, males are expected to develop BCCs on the trunk owing to their high level of occupational sun exposure, lack of protective clothing on the trunk during UV exposure and lack of use of sunscreens, the results seen in our study could be explained by recreational sun exposure in our female patients as well as inadequate use of sunscreens which is prevalent in adult patients (Andrade et al, 2012; Buller et al, 2011).

More males (14.4%) had their BCCs located on the lower extremities than females (3.8%). This is contrary to the international literature, where females are more likely to get NMSCs on the lower limbs compared to males (Buettner and Raasch, 1998). This is because traditionally, women wear skirts and men wear long trousers and thus the lower limbs in females are more likely to be exposed to the sun compared to males. The results obtained in our study could be explained by the change in dressing habits in both males and females (Andrade et al, 2012).

4.4. Distribution of SCC in males and females according to tumour site

In our study, there was a statistically significant difference in the body site of SCCs between males and females (p=0.014).

As in BCCs, the majority of SCCs in males (83.3%) and females (53.3%) were located on the sun exposed areas of body (head and neck region and upper extremities) as depicted in figure 3.3. This is in keeping with both local and international findings, where the common location of SCC are the body areas that are chronically exposed to ultraviolet radiation (Norval, Kellet and Wright, 2014, Andrade et al, 2012, Buettner and Raasch, 1998).

As opposed to males, where only 6.7% of patients had their SCC located on the lower limbs, a large number of females (20%) had their SCCs located on the lower limbs. The occurrence of more SCCs on lower limbs in females compared to males is similar to the findings of a study done by Buettner and Raasch (1998), where women were reported to have more SCCs located on the legs than men. This is again thought to be due to different clothing habits for males and females. In addition, the occurrence of SCCs on the legs of women in this study could be attributed to an increased likelihood of trauma and development of chronic wounds on the exposed lower limbs of women, which is a known risk factor for development of SCCs (Norval, Kellet and Wright, 2014, Diepgan and Mahler, 2002, Halder and Bang, 1988).

As shown in figure 3.4, a significant number of females (20%) had their SCCs located at other sites such as the buttocks and genitalia, compared to their male counterparts (5%). The occurrence of SCCs in these areas that are not exposed to the sun can be explained by the presence of other risk factors such as HPV infections and HIV infection. This figure is much higher than the findings reported in international literature (Andrade et al, 2012, Buettner and Raasch, 1998). This high number could be explained by the high prevalence of HIV in South Africa (UNAIDS, 2006).

4.5. Histologic subtypes of BCCs

The most common histologic pattern of BCC in our study was a mixed histologic pattern, which accounted for approximately 30% of the cases. This was followed by nodular BCC (16.5%) and the superficial type of BCC (10.2%). This figure is similar to that reported in the international literature, where the mixed histologic pattern, nodular BCC and superficial BCC were reported as the three most common histologic subtypes of BCC (Sexton, Jones and Maloney, 1990).

The nodular histologic subtype is speculated to be associated with chronic sun exposure. The fact that this is one of the commonest histologic types of BCC in our patients could be explained by intense chronic ultraviolet radiation exposure to the harsh South African sun (Raasch, Buettner and Garbe, 2006, Wright et al, 2012).

On the other hand, the superficial histologic subtype of BCC is said to be associated with intermittent sun exposure in form of sunburn, particularly during childhood. A significant number of our patients had their BCCs located on the trunk (12.4%), a site that usually suffers from sunburn, which could explain the high prevalence of this histologic subtype in our patients (Raasch, Buettner and Garbe, 2006; English et al, 1998, Kricker, Armstrong and English, 1994, Kricker et al,1995).

The morpheic histologic subtype in our study was slightly more common than that reported by Sexton, Jones and Maloney (1990), accounting for 7.1% of the cases, as opposed to only 1% of the cases reported in Sexton, Jones and Maloney (1990). This large number of morpheic histologic subtype can also be explained by the chronic sun exposure in South African patients, as most morpheic BCCs are reported to occur on the sun exposed areas of the body (Scrinever, Grosshans and Cribier, (2002).

4.6. Histologic subtypes of SCCs

The majority of SCCs in our study were of the conventional histological subtype: moderately differentiated, accounting for 58.9% of the cases, well differentiated SCCs (24.4%) and poorly differentiated SCCs (5.6%). This is in keeping with studies published in literature, where the conventional histologic subtype of SCC was reported as the major histologic subtype of SCC (Lohman and Solomon, (2001), Yanofsky, Mercer and Phelps (2011). There is, however, paucity in literature with

regards to studies enumerating the exact figures of different histologic subtypes of SCCs.

4.7. Other risk factors associated with development of NMSCs

As previously stated, the majority of our patients in our study had no specified risk factors (91%). This could be due to failure by the clinicians to specify risk factors present when completing histology requisitions, or it could be that the majority of the patients in this study are probably fair skinned individuals with no additional risk factors that predispose them to developing NMSCs.

Of the patients with NMSCs and specified risk factors on histology reports, 3.7% had oculocutaneous albinism (OCA). Most of the patients with OCA were also young (majority below age 40 years) compared to other patients with no specified risk factor. Black patients with OCA are at increased risk of developing NMSCs, particularly SCCs, at an early age. OCA is reported to be prevalent in sub-Saharan Africa, including South Africa (Shapiro et al, 1953; Lekalakala et al, 2015). XP was reported in 2 of the patients with NMSCs in our study. These two patients were both below 20 years of age, and as reported in literature, developed NMSCs at a very young age (Jaju et al, 2016).

Organ transplant patients accounted for 2.5% of all patients with NMSCs. This is in keeping with reports published in international literature, where organ transplant

patients on immunosuppressive agents are reported to be at increased risk of developing NMSCs (Marzuka and Book, (2015).

Surprisingly, only three patients (0.8%) of all patients with NMSCs in our study had HIV. HIV is prevalent in South Africa, and a much higher number of patients with HIV and NMSCs than this was expected (UNAIDS, 2006). This low figure most likely reflects the fact that the HIV status of patients in our study was omitted and not recorded in the histology reports. All three patients with HIV in our study had SCCs. This is in keeping with findings reported by Silverberg et al, where HIV was reported to increase the risk of developing SCCs and not BCCs (Silverberg et al, 2013).

In our study, it is difficult to quantify HPV infections in these patients as HPV subtyping was not done. It is assumed that NMSCs, particularly SCCs, located in the genital areas are most likely to be associated with HPV infections (Hasche et al, 2017). Three patients in this study also had epidermodysplasia verruciformis. Patients with EDV have a genetic mutation that makes them susceptible to HPV infections and subsequent development of NMSCs, particularly SCCs (Burger and Itin, (2014), de Jong et al, 2018; Gul et al, 2007).

CHAPTER 5: CONCLUSION AND REMOMMENDATIONS

5.1. Conclusion

The important conclusions derived from this retrospective case review of laboratory reports of histologically confirmed NMSCs of patients attending Helen Joseph Hospital and Charlotte Maxeke Johannesburg Academic Hospital are:

- In keeping with international trends, basal cell carcinoma (BCC) was the most common NMSC encountered in patients attending these two academic hospitals.
- As described in the international and local literature, the majority of NMSCs in our study occurred in elderly, male patients.
- Unfortunately, the race/ ethnicity of the majority of patients was omitted from the histology reports, making it difficult to determine the race of the patients in which these NMSCs were observed.
- In keeping with studies done on predominantly Caucasian populations, most NMSCs in our patients were located on the sun-exposed areas of the body.
- BCCs located on the trunk were observed more in females than in males. This is contrary to the international trends, where BCCs located on the trunk were predominantly observed in male patients. This trend in our study can be attributed to recreational exposure to UV radiation in our female patients, as well as inadequate use of sunscreens which is prevalent in adult patients.
- More males had BCCs located on the lower limbs than their female counterparts. This is contrary to the international literature, where females are more likely to get NMSCs on the lower limbs compared to males. This result can be attributed to the change in dressing habits in both males and females,

where males, particularly South African white, male farmers tend to wear shorts, whilst more females are now opting to wear trousers.

- In keeping with international trends, a significant number of females had SCCs located on the legs.
- Contrary to international trends, more females had SCCs located on non-sun exposed areas of the body, such as the genitalia and buttocks. The occurrence of SCCs in these areas that are not exposed to the sun can be explained by the presence of other risk factors such as HPV infections and HIV infection. In our study, the high number of SCCs occurring on the buttocks and genitalia in females could be attributed to the high prevalence of HIV in South African women compared to their male counterparts.
- Similar to international trends, a mixed histologic pattern, which is associated with aggressive clinical behavior, was the most common histologic subtype of BCC observed in our study.
- In keeping with international trends, most SCCs were moderately differentiated invasive SCCs. This predominant histologic subtype observed in our study is associated with intermediate clinical behavior.
- Additional risk factors implicated in the development of NMSCs observed in our patients included OCA, EDV, XP, organ transplant patients, and HIV infection.
- Although HPV infection has not been directly observed as a risk factor for development of NMSCs in this study, it has been implicated as a causative agent in the development of SCCs, particularly in the genital and buttock areas.

- Although very few patients had their HIV status recorded on the histology reports in our study, it is apparent that HIV is a risk factor for the development of SCC and not BCC. This is in keeping with findings described in international literature, where HIV was reported to increase the risk of developing SCCs and not BCCs.

5.2. Recommendations

- The findings of this study highlight the need for clinicians to examine patients on a regular basis, and biopsy all skin lesions suspicious of NMSCs and send them for histological diagnosis.
- It also highlights the need for clinicians to provide detailed information, particularly the race, the HIV status and presence of other risk factors, when completing the histology request form. This will improve the quality of similar studies in the future.
- Pathologists are encouraged to provide the histologic subtypes of NMSCs, as these play an important role in the prognosis and management of patients.
- There is a need for the South African Cancer Registry to keep record of all histologically confirmed NMSCs, as this will aid in data collection for future research.
- There is also a need for the private sector to be included in the future research of NMSCs, as demographically, these cancers are probably more common in this sector, compared to the public sector where this study took place.

- Patients irrespective of their race, should be encouraged to use sunscreens on a regular basis, starting from childhood. They should also be encouraged to adopt other sun protective behavior such as wearing protective clothing and avoidance of midday ultraviolet solar radiation.
- Patients, particularly female patients, should be educated on prevention, early diagnosis and treatment of HIV and HPV infections, as this may result in reduced prevalence of SCCs of the genitalia and buttocks in these patients.
- As this is the first study on NMSCs, according to the knowledge of the author, to be conducted in these two hospitals, further research on NMSCs is required, as this will help with allocation of healthcare resources required to diagnose, treat and prevent NMSCs.

CHAPTER 6: REFERENCES AND APPENDICES

6.1. References

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6.2. Appendices

R14/49 Dr Julia Ndakunda

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170236

NAME: (Principal Investigator)	Dr Julia Ndakunda
DEPARTMENT:	Dermatology Charlotte Maxeke Johannesburg Academic Hospital Helen Joseph Hospital National Health Laboratory Service
PROJECT TITLE:	A Descriptive Study of Non-Melanoma Skin Cancers in Patients Attending Charlotte Maxeke Johannesburg Academic Hospital and Helen Joseph Hospital from July 2013 to June 2016
DATE CONSIDERED:	24/02/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Deepak Modi
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	27/02/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in February and will therefore be due in the month of February each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES