A Descriptive retrospective study of non-melanoma skin cancers in African patients with albinism at Chris Hani Baragwanath Academic Hospital.

July 2015 – June 2017

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A research report submitted to the University of The Witwatersrand, Johannesburg in partial fulfilment for the requirements of the degree of Master of Dermatology 2020.

DECLARATION

I, S'lindile Omega Buthelezi, declare that this research project is my own work which is being submitted for the degree of Master of Medicine in the branch of Dermatology at the University of Witwatersrand, Johannesburg.

It has not been submitted before for any examination or degree at this or any other University.

Signature:

S.O Buthelezi:

Date: 01 September 2020

ACKNOWLEDGEMENTS

I would like to thank God almighty for the wisdom and strength to complete this project. “I can do all things through Christ who strengthens me” Phil 4:13

I would also like to thank my supervisors, Professor E. Ndobe and Dr S. Sibisi for their time, patience and academic guidance in completing this project.

I’m grateful to Ms Helen Nxumalo for patiently helping me trace biopsy results

A special thank you to all my friends and family, particularly my two sisters who are my biggest cheerleaders and constantly pray for me.

My son, Alinde for his unconditional love and patience while I worked on this project.

My son’s nanny, Stella for playing the role of his second mom while I worked on this project.

ABSTRACT

Background

Oculocutaneous albinism (OCA) is an autosomal recessive genetic disorder characterised by reduced or absent melanin pigment in the skin, eyes and hair. The most serious sequelae are gross visual disturbances and development of skin cancers. Albinism patients develop pre malignant and malignant lesions at an earlier age compared to normal population. Albinos living closer to the equator are at a higher risk of non-melanoma skin cancers.

The skin is the largest organ in the human body. It is therefore the commonest site for cancers. The majority of skin cancers are non-melanoma skin cancers, namely basal cell carcinomas (BCC) and squamous cell carcinomas (SCC). They account for 20-30% of neoplasms seen in Caucasians and 1-2% in coloured skin. Chronic sun exposure is the major contributing factor to developing these skin cancers. (Kennedy et al, 2003) According to Kricker at al, sun exposure may be less important in the development of BCC's compared to SCC's. There are other risk factors to developing non-melanoma skin cancers. These include environmental and genetic risk factors. (Kennedy et al, 2003)

Unfortunately the exact prevalence of non-melanoma skin cancers in the South African albinism population is not known. Limited studies have been done in Africa which described the prevalence of skin lesions and skin cancers affecting the albinism population.

Objectives

To determine the number of patients with basal cell carcinomas, squamous cell carcinomas and other non-melanoma skin cancers in both sexes, different age groups, tumour sites in patients with albinism attending Chris Hani Baragwanath Academic Hospital.

Methods

This study is a retrospective study of laboratory reports of histologically confirmed skin cancers of patients attending Chris Hani Baragwanath Academic Hospital, whose skin biopsy specimens were submitted to the National Health Laboratory Service at Chris Hani Baragwanath Academic Hospital from July 2013 to June 2017. The histology reports provided demographic data and whether the patient has albinism or other risk factors for skin cancers. The report also provided a description of the clinical lesions and site of the lesion. The report also provides a histologic subtype of the skin cancer.

Results

A total of 50 patients with albinism with confirmed NMSCs on histopathology reports were studied. The study showed a female predominance with 60% patients being female and 40% male. The youngest patient was 19 years old and the oldest was 81 years old. The mean age was 45.44 year and the median age was 43 years from the sample of 50 patients. Out of the 50 patients, 32 patients had Basal cell carcinomas (64%), 26 patients had Squamous cell carcinomas (52%) and 2 patients had Bowens disease (4%). The commonest site was the head and neck region for all types of skin cancers.

Conclusion

The prevalence of skin cancers in albinism patients is overwhelmingly high. Basal cell carcinomas are predominant over squamous cell carcinomas. Unfortunately there is not enough studies to describe the exact prevalence in South Africa. The last study done in Johannesburg was in 1989. There is still a need to raise awareness and educate African patients on sun protection and sun avoidance as well as early diagnosis and aggressive management of pre malignant lesions.

ABBREVIATIONS

OCA	Oculocutaneous Albinism
NMSC	Non melanoma skin cancers
BCC	Basal cell carcinoma
SCC	Squamous cell carcinoma
PUVA	Psoralen and ultraviolet A (PUVA)
MCR-1	Melanocortin-1 receptor
HIV	Human immunodeficiency virus
PDT	Photodynamic therapy
UVR	Ultraviolet radiation

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INTRODUCTION

OCULOCUTANEOUS ALBINISM

Oculocutaneous albinism (OCA) is an autosomal recessive genetic disorder characterised by reduced or absent melanin pigment in skin, eyes and hair.(Gronskov et al., 2007) The most serious sequelae are gross visual disturbances and development of skin cancers. Albinism patients develop pre malignant and malignant lesions at an earlier age. The mean age of developing malignancies is 35 years.(Kiprono et al., 2014) There are seven clinical subtypes of OCA described in the literature. Based on molecular studies, four types have been defined. These are OCA1, OCA2, OCA3 and OCA4.(Gronskov et al., 2007) They are classified according to the genetic mutation. OCA1 and OCA2 are the most common subtypes. In OCA1 there is lack of tyrosine kinase due to TYR gene mutation. It accounts for 40% of OCA worldwide. It is the most severe and most common in Japan, non-Hispanic Caucasians and mixed race European populations. Its prevalence is 1:40, 000 in these populations.(Marcon and Maia, 2019) It is very rare in the black population. Some of these patients have a complete lack of enzyme activity and the pigment remains completely absent throughout their lives. Certain patients develop some pigment with age and ocular changes are less severe in these patients. (Manga et al, 2013)

In OCA2 there is a mutation in the P gene, on chromosome 15q11-12. This results in a lack of activity of P protein which regulates the pH in melanosomes where tyrosinase acts. OCA2 is most common in Africa.(Gronskov et al., 2007). OCA2 has a worldwide incidence of 1 in

36000. In Africa, Tanzania has one of the world's highest rates of albinism at a frequency of 1 in 1400. The rate in Cameroon is 1 in 7900 and in South Africa 1 in 3900. Some of these patients are born with some pigmentation and pigmentation improves slightly with age. Some patients develop freckles on sun exposed areas and the ocular changes are usually less severe than in OCA1.(Manga et al., 2013)

In OCA3 (Also known as Rufous OCA), there is a mutation in the TYRP1 gene, located on chromosome 9p23. This gene is responsible for maintaining melanosome structure and melanocyte proliferation. The prevalence of OCA3 is estimated to be 1 in 8500 albinos in Southern Africa. There is no data available on its prevalence in South Africa. These patients have red hair with reddish-brown skin. Their susceptibility to skin damage and skin cancers is lower than for OCA2.(Manga et al., 2013)

In OCA4, there is a mutation in the MATP gene. This gene encodes a membrane associated transporter protein. This has a role in tyrosinase processing and trafficking of proteins. This phenotype is characterised by hypopigmentaion of hair and skin with ocular changes similar to the others. (Marcon and Maia, 2019)

The worldwide prevalence of OCA4 is estimated to be 1 in 100,000. It is most common in Japan. It has also been described in German, Turkish and Chinese and Danish born patients. It has not been described in Africa.(Hayashi and Suzuki, 1993)

NON MELANOMA SKIN CANCERS

The skin is the largest organ in the human body. It is therefore the commonest site for cancers. The majority of skin cancers are non-melanoma skin cancers, namely basal cell carcinomas (BCC) and squamous cell carcinomas (SCC). They account for 20-30% of neoplasms seen in Caucasians and 1-2% in coloured skin. (Kiprono et al, 2014)

The skin is made up of three layers, namely the epidermis, dermis and subcutaneous fat. The epidermis, which is the outer most layer and is therefore most exposed to the sun and other environmental elements. (Colegio et al., 2018)

This layer contains four major cell populations: keratinocytes, melanocytes, Langerhans cells and Merkel cells. Keratinocytes make up the majority of the cell populations. These originate in a stem cell pool in the basal layer and undergo differentiation and maturation as they migrate upward to form the stratum corneum.(Colegio et al., 2018) Non melanoma skin cancers are cancers derived from the keratinocytes of the epidermis.(Colegio et al., 2018) Chronic sun exposure is the major contributing factor to developing these skin cancers. (Kennedy et al, 2003) According to Kricker at al, sun exposure may be less important in the development of BCC's compared to SCC's. There are other risk factors to developing non-melanoma skin cancers such as phenotype, pre-existing genetic syndromes and precursor lesions. These include environmental and genetic risk factors. (Kennedy et al, 2003) Environmental factors include other types of UV exposure e.g. psoralen and ultraviolet A (PUVA) and suntan beds.

Phenotypic characteristics such as red hair, freckling and poor ability to tan have been identified as risk factors. A key gene called the MC1R gene encodes the human melanocortin-1 receptor (MC1R). Mutation of this gene is responsible for red hair/fair skin, which is known to increase the risk of cancers in these patients.(King et al., 2003) (Colegio et al., 2018)

In addition to sun exposure and genetic disorders, immunosuppression also increases the risk of developing non-melanoma skin cancers such as organ transplants. Exposure to chemical carcinogens such as arsenic and tobacco also contribute to the development of skin cancers. (Murzuka et al, 2015; Diepgan et al, 2002) Several medical conditions are also implicated in the risk for developing non-melanoma skin cancers such as human immunodeficiency virus (HIV) infection, human papilloma virus (HPV) infection and chronic marjolin's ulcers that

develop on chronic scars such as burn scars. HIV infected patients have been reported to have a 3 times higher rate of non-melanoma cancers compared to the general population.

UV exposure combined with these genetic and other factors leads to cell damage, DNA damage and failure to repair DNA which leads to accumulation of damaged DNA and malignant transformation.(Trakatelli et al., 2007) One of the genetic risk factors is Oculocutaneous Albinism. See figure 1, page 5 for pathogenesis

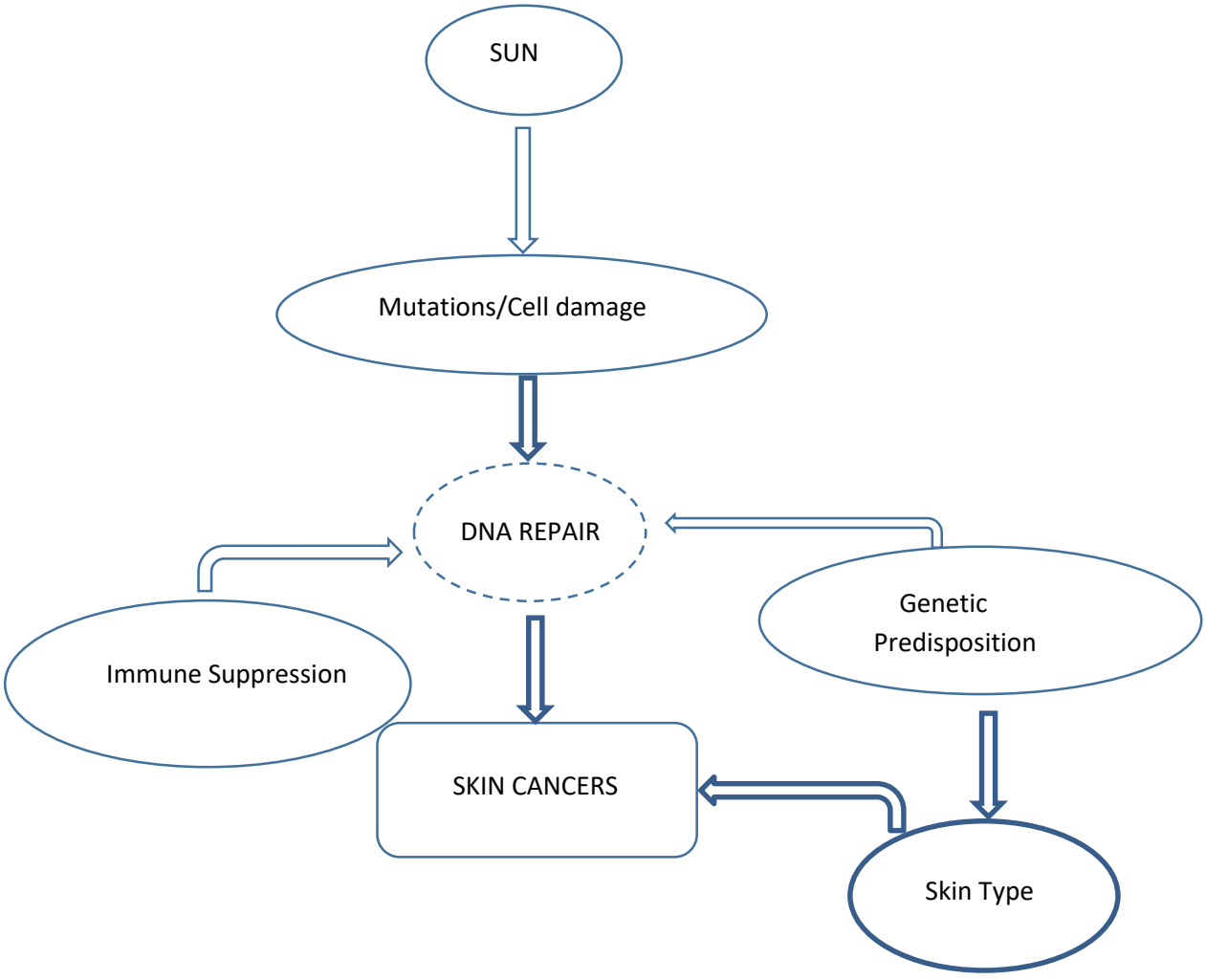

Figure 1.1: pathogenesis of NMSCs

CLASSIFICATION

BASAL CELL CARCINOMAS

Basal cell carcinomas are derived from the keratinocytes of the basal layer. They are the most common non melanoma skin cancers (NMSCs) in countries with largely white skinned population. They make up approximately 80% of NMSCs. It is estimated to account for approximately 2 million new cases of skin cancers reported per year. (Marzuka and Book, 2015) The pathophysiology of BCCs is multifactorial. Intermittent sun exposure in childhood play a major role in its pathogenesis. The ultraviolet radiation (UVR) exposure causes DNA damage and mutation in tumour suppressor genes. Other factors include oxidative stress and inflammatory response to UVR damage.(Colegio et al., 2018) Activation of the sonic hedgehog signalling pathway (SHH) plays an important role in the development of BCCs. The hedgehog family is crucial for growth, differentiation, morphogenesis and function of various cells and organs.(Colegio et al., 2018)

Risk factors

- Fair skin type (I–II)
- Intermittent UV exposure
- Tanning studio visits
- > 6 sunburns

Exposure to

- Arsenic
- Coal tar
- Ionizing radiation

Genodermatoses

- Oculocutaneous Albinism
- Xeroderma pigmentosum
- Gorlin-Goltz syndrome
- Bazex-Dupré-Christol syndrome
- Rombo syndrome
- Multiple familial trichoepitheliomas

Immunosuppression `

- Organ transplant patients
- HIV infection

Radiodermatitis

Marjolin's ulcers on chronic scars

CLINICAL FEATURES

There is more than 26 different subtypes of BCCs described in literature. There is still no universally accepted classification scheme. There are four main characteristic clinicopathologic types, namely nodular, superficial, morpheaform and fibroepithelial. There may be an overlap of theses subtypes and ulceration is more common in the nodular types compared to the others. Majority of BCCs are amelanotic. Pigmented BCCs are seen commonly in individuals with darker pigmented skin. (Marzuka and Book, 2015)

Nodular BCCs is the most common subtype, accounting for 50% of all BCCs. They typically presents as a shiny, pearly papule or nodule with a smooth telangiectatic surface with variable pigmentation. There may be secondary ulceration. There is often a rolled, raised border. They often favour sun exposed areas, like face, especially forehead, nose and cheeks. They may

arise in any hair bearing areas of the skin. Rarely seen on non-hair bearing sites.(Soyer et al., 2018)

Superficial BBCs typically present as a well circumscribed erythematous macule or thin papule or plaques. Lesions often grow horizontally, occasionally becoming deeply invasive with induration, ulceration and nodule formation. With secondary scale and crust with thin rolled borders and variable amounts of melanin in larger lesions. They may present with areas of regression characterised by atrophy and hypopigmentation. This subtype favours the trunk and it is the most common in younger patients. (Soyer et al., 2018)

Morpheaform BBCs are a less common subtype frequently presenting as slightly raised to depressed area of induration that is usually pale pink to white in colour with ill-defined border resembling a scar or morphea. Secondary crust, scale and erosion is uncommon.(Soyer et al., 2018)

Fibroepithelial BCCs are a rare variant presenting with a skin coloured or pink sessile plaque or nodule often pedunculated with a smooth surface. They favour the trunk and are more common in individuals with multiple BCCs. (Soyer et al., 2018)

All BCCs are histologically characterised by basaloid keratinocytes with a variably fibromyxoid stroma. The cells have large uniform nuclei and scant cytoplasm with indistinct desmosomes. (Soyer et al., 2018)

Table 1.1: Histological variants of BCCs

Nodular	Solid Large round/oval islands of basaloid cells with retraction artefact, peripheral palisading of nuclei.
Superficial	Small buds of tumor cells extending from epidermis to the dermis.
Morpheaform	Highly likely to be infiltrating or aggressive, thin strands of basaloid cells in fibrotic stroma.
Fibroepithelial	Thin anastomosing basaloid cells in loose stroma, multiple connections to epidermis.
Basosquamous	Combined features of basal and squamous cell carcinoma.
Cystic	Cystic space within tumor nodules, usually due to necrosis or mucin production.

(Rapini, 2012, Soyer et al., 2018)

SQUAMOUS CELL CARCINOMAS

Squamous cell carcinomas (SCCs) are malignant tumours of epidermal keratinocytes that invade the dermis. It is the second most common type of NMSCs. The exact incidence of SCCs is difficult to determine due to inadequacy in diagnosis and overlap with other conditions like actinic keratosis. The commonest cause is UVR exposure. Long term exposure to the sun is the major risk factor.(Rigel, 2008) Therefore, sun exposed areas are favoured. The risk increases with the increase in annual UVR exposure. Other risk factors include immunosuppression. The risk of cutaneous SCCs is greatly increased, by up to 250 fold in renal transplant patients on azathioprine.(Colegio et al., 2018)

Other risk factors include chronic ulcers, chronic scaring, hidradenitis suppurativa, previous radiation exposure, PUVA and genodermatoses. The mortality and metastatic rate is low. It is

estimated to be 18% on sun exposed areas and 20-30% on chronic scarring. (Colegio et al., 2018)

CLINICAL FEATURES

Actinic keratosis is the commonest precursor of SCCs on sun exposed areas. The dorsum of the hands is the commonest site. The lesions are often superficial, discrete and hard on an indurated base. The lesions progress to large, deep ulcerated nodules. The lesions are localised, raised and mobile in the early phases and gradually become diffuse, and fixed. It eventually invades underlying structures. The surface of older lesions may resemble a cauliflower with filamentous projections and a purulent, malodourous exudates in between them.(Soyer et al., 2018) SCCs are 20% more common in black patients than BCCs. Elderly patients are primary affected on lower legs. This is thought to be most likely due to exposure to open fires.(Soyer et al., 2018) In white patients the most common predisposing conditions are scarring processes.

SCCs of the lips are often preceded by actinic cheilitis. The vermillion border becomes dry and fissured. In early SCC lesions, localised thickening is seen which then progresses to a firm nodule and tumour. Smoking is also a predisposing factor. The lower lip is more affected than the upper lip. (Ridky, 2007, Soyer et al., 2018)

Histology

The histology of SCCs is characterised by the nest, cords and sheets of neoplastic cells extending to and invading the dermis.

Thickness is an important marker of metastasis. Thickness of 2mm is associated with a metastatic rate of 4% and a thickness of 6mm with a rate of 16%. Lesions on the ear, immunosuppression and increase horizontal size all increase the risk of metastasis by two to four fold.

Table 1.2: Histological variants of SCCs

Well differentiated SCC,	Characterized by pale and glassy cell and less atypical. More keratin pearls
The poorly differentiated SCC	Are more aggressive and infiltrating with more severe aytipia. The cells are less pale and glossy with fewer keratin pearls.
Adenoid/acantholytic SCC	is an aggressive type characterised by acantholysis and gland like changes
Adenosquamous cell Carcinoma	Very rare and aggressive subtype. Characterized by goblet cells containing mucin similar to sweat gland carcinomas.
Spindle cell SCC	Aggressive subtype with prominent spindle cells and less keratinization
Verrucous carcinoma	Characterized by well differentiated verrucous proliferation with very little atypia.
Lymphoepithelioma-like carcinoma	Very rare variant with islands of epithelial cells obscured by lymphocytic infiltrate.

(Rapini, 2012, Soyer et al., 2018)

Treatment

Treatment of choice for SCCs is surgical excision.(James et al., 2016) Photodynamic therapy (PDT) may be useful to reduce the number of SCCs in areas of previous sun damage. Systemic retinoid have a role in reducing the risk of SCCs in patients with existing predisposing conditions such as epidermodysplasia verruciformis. High risk patients should be educated

about sun avoidance and sun protection, with the use of broad spectrum sun screens with physical blockers. These patients should have regular skin examinations by a dermatologist. The use of Sirolimus has been associated with a decreased risk of SCCs in organ transplant patients compared to immunosuppressants. (Soyer et al., 2018, Marzuka and Book, 2015)

TRENDS IN EPIDEMIOLOGY IN AFRICA

According to Kiprono et al in a study done in Tanzania in 2014, non-melanoma skin cancers are overwhelmingly prevalent in the albinism community. The proportion of squamous cell carcinomas and basal cell carcinomas is similar, contrary to previous studies that reported a predominance of squamous cell carcinomas in albinos.(Mabula et al., 2012) Unfortunately the exact prevalence of non-melanoma skin cancers in the South African albinism population is not known. The last study done in Johannesburg, South Africa was by Kromberg et al in 1989 which found that SCCs were more frequent than BCCs. Studies have shown that Albinos living closer to the equator develop sun damage and malignancies by the second decade of life.(Kiprono et al., 2014) South Africa's annual average temperature is 22 degrees Celsius with very high UV index all year round, making South Africans, particularly at high risk of sun damage and non-melanoma skin cancers.(Norval et al., 2014) Albinos in Africa tend to have a worse prognosis with skin cancers compared to other parts of the world because of late presentation to health care facilities and poor treatment compliance due to poor economic circumstances.(Mabula et al., 2012)

This research aims to describe the characteristics of SCC's and BCC's in Albinos attending Chris Hani Baragwanath Academic Hospital. According to recent literature, this type of study has never been done in this hospital or in Johannesburg, South Africa. Knowing the characteristics of these skin cancers will help determine the morbidity and mortality associated with these skin cancers, as well as the burden these cancers place on the health care resources.

This in turn will help in re-allocation of health care resources to implementation of skin cancer preventive strategies, such as community education drives to raise awareness of the condition and the importance of preventing complications by use of sunscreens and protective clothing, sun exposure avoidance, as well as early detection and treatment of non-melanoma skin cancers. In addition to the various cutaneous disorders associated with albinism, there is a myth in most African countries that the body parts of albinos can be used in potions believed to be magical, placing an additional threat on individuals afflicted with this condition.(Brilliant, 2015)

STUDY OBJECTIVES

Primary objective

1. To determine the number of patients with basal cell carcinomas, squamous cell carcinomas and other non-melanoma skin cancers in both sexes, different age groups, tumour sites (head and neck, upper extremities, lower extremities, trunk or other sites) in patients with albinism. The data will be based on history, relevant clinical findings on histology reports.

Secondary objectives

1. To compare the numbers and percentages of BCC's and SCC's in males and females and sites commonly affected eg (head and neck, upper extremities, lower extremities, trunk or other sites).

2. To document different histologic subtypes of BCC's and SCC's (eg. Superficial, nodular, cystic, etc)

METHODOLOGY

Study design

This study is a retrospective study of laboratory reports of histologically confirmed skin cancers of patients attending Chris Hani Baragwanath Academic Hospital, whose skin biopsy specimen was submitted to the National Health Laboratory Service at Chris Hani Baragwanath Academic Hospital from July 2013 to June 2017.

The histology reports provided demographic data (age, gender), whether the patient has albinism or other risk factors for skin cancers, as well as the HIV status of the patient. The report also provided a description of the clinical lesions and site of the lesion. The clinical description is then matched with the histological description of the suspected cancer. The report also provides a histologic subtypes of non-melanoma skin cancer.

Study Population

Inclusion criteria

1. All histologically confirmed non-melanoma skin cancers recorded from 1 July 2013 to 30 June 2017 at Chris Hani Baragwanath Academic Hospital.
2. All age groups will be recorded

Exclusion criteria

1. Laboratory confirmed non-melanoma skin cancers in non-albinism patients.
2. Laboratory records of non-melanoma skin cancers outside the period between July 2013 and June 2017.
3. Laboratory reports not conclusive of malignancy.

DATA PROCESSING AND ANALYSIS

Data was captured on research data collection sheet and then transferred to excel.

The package used for the quantitative analysis was the Statistical Package for Social Sciences (SPSS) version 25 software, where descriptive tables and graphic presentations were generated to answer the research questions. Data was then cleaned to check for missing variables.

LIMITATIONS

1. Not all non-melanoma skin cancers particularly basal cell carcinomas are biopsied and sent for histology, and not all people with non-melanoma skin cancers visit hospitals. As a result, the exact number of these skin cancers may be underestimated.
2. Some of the histology reports did not specify if the patient has albinism, and thus were left out of the study.
3. Missing data and inconclusive laboratory reports such unspecified site of the cancer and histological subtype as well as the patient's HIV status.

ETHICS

Permission to conduct the study was obtained from the acting head of department of Dermatology at Chris Hani Baragwanath Academic Hospital and the CEO of Chris Hani Baragwanath Academic Hospital. Permission to access and use laboratory data was obtained from the head of department of Anatomical Pathology of the NHLS laboratory based at Chris Hani Baragwanath Academic Hospital.

The study proposal was approved by the Human Research Ethics Committee of the University of Witwatersrand. To protect participant's confidentiality, the data was sent in an anonymised

format with each patient being allocated a special number, making patient identification unlikely. The data was sent and stored in a password protected device.

FINANCE

The study was self-funded

Item	**Estimated cost in Rands**
Printing	600
Binding	400
Total	1000

SCHEDULE

	March 2018-May 2018	June 2018-July 2018	August 2018-July 2019	Aug 2019-Sept 2019	Nov 2019-Dec 2019	Jan 2020-Feb 2020
Research protocol						
Assessment & Ethics application						
			Part 2 studies			
Data collection						
Data analysis						
Writing up						

CHAPTER 2

RESULTS

Descriptive and Frequency

A total of 50 patients with albinism were identified with cutaneous NMSCs confirmed on histopathology among biopsies diagnosed with NMSCs at Chris Hani Baragwanath Academic Hospital between the 1st of July 2013 and 30th of June 2017. The exact prevalence is therefore difficult to assess as there were a number of reports that did not specify whether the patients had albinism.

Demographics

1. Age

   The patients' ages were recorded. The mean age was 45.44 years with a standard deviation of 14.187 from the sample of 50 patients studied. The youngest patient was 19 years old and the oldest was 81 years old.

2. Gender

   The gender of the patients was recorded. The results shown in the graph below reflect the findings: there are 20 males (40%) and 30 females (60%) in the sample.

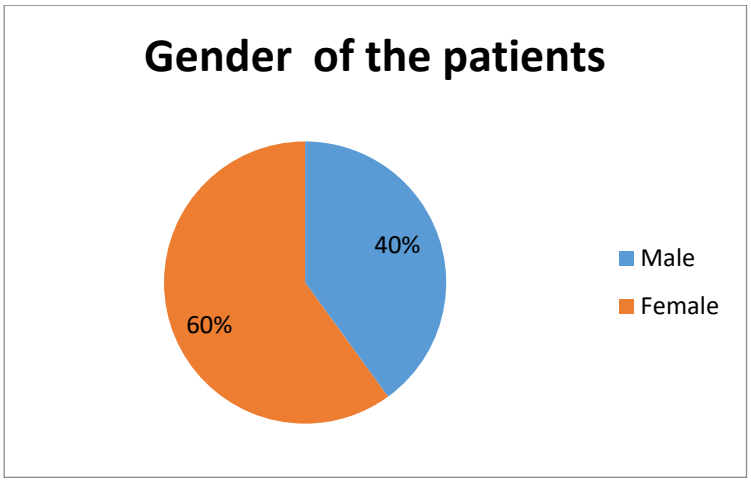

Figure 2.1: Gender of the 50 patients

CLINICAL CHARACTERISTICS

3. TYPE OF SKIN CANCER

The patients' type of skin cancer was recorded. 60 cancers were studied out of the 50 patients, as the patients can have one or more types. The results are presented in table 1 as follows: 32 patients had Basal cell carcinoma (BCC) (64%), 26 patients had Squamous cell carcinoma (SCC) (52%) and 2 patients had Bowens disease (4%).

The results also show that 7 (14%) patients had both BCCs and SCCs, 1 (2%) patient had Squamous cell carcinoma and Bowens disease and 1 (2%) patient had the three types of skin cancers.

Table 2.1: Types of skin cancer

Morphology of lesions	Cancers studied		Percentage of Patients
	n	Percentage	
Basal cell carcinoma	32	53.3%	64%
Squamous cell carcinoma	26	43.3%	52%
Bowens disease	2	3.3%	4%
Total	**60**	**100,0%**	**120%**

4. SITE OF SKIN CANCER

The site of the cancer on the patients' body was commented on and 63 options were selected as the patients can have one or more sites involved with the cancer(s). The results in the table reflect the findings:

36 of the patients had the cancer located in the head and neck region (72%), 14 patients located on upper extremities (28%), 9 patients located on lower extremities (18%), 3 patients located on the trunk (6%) and 3 patients with an unspecified site. (6%).

The results also show that 38 (76%) patients had one site of the cancer(s), 9 (18%) patients had two sites of the cancer(s) and 3 (6%) patient had three sites of the cancer(s).

Table 2.2: Site of skin cancer

Site of skin cancer	Cancers studied		Percentage of patients
	n	Percentage	
Head and neck	36	55.4%	72%
Upper extremities	14	21.5%	28%
Lower extremities	9	13.8%	18%
Trunk	3	4.6%	6%
Unspecified	3	4.6%	6%
Total	**65**	**100.0%**	**130.0%**

5. HISTOLOGIC SUBTYPES

BCC

The histologic subtypes were recorded. The first was the BCC. 34 BCCs were studied as the patients can have one or more histological subtypes. The results in the table reflect these findings: 13 of the patients had the nodular type (40.6%), 9 patients had the superficial type (28.1%), 5 patients had the basosquamous type (25.6%), 3 patients had the morpheaform type (9.4%), 2 patients had the micronodular type (6.3%) and 2 patients had an unspecified type (6.3%).

Table 2.3: BCC subtypes

BCC	Cancers studied		Percentage of patients
	n	Percentage	
Superficial	9	26.5%	28.1%
Basosquamous cell	5	14.7%	15.6%
Nodular	13	38.2%	40.6%
Morpheaform	3	8.8%	9.4%
Micronodular	2	5.9%	6.3%
Unspecified	2	5.9%	6.3%
Total	**34**	**100.0%**	**106.3%**

SCC subtypes

There was a record of the SCC subtypes of 27 (54%) patients. The results shown in table 2.4 reflect the findings; 8 (29.6%) patients had poorly differentiated SCC, 5 (18.5%) patients had moderately differentiated SCC, 9 (33.3%) patients had well differentiated SCC and 5 (18.5%) had unspecified type of SCC

Table 2.4: SCC subtypes

SCC	Frequency	Percentage
Poorly differentiated	8	16%
Moderately differentiated	5	10%
Well differentiated	9	18%
Unspecified	5	10%
Total	**27**	**54%**

Table 2.5: Type of cancer by Gender

Gender	Type of Cancer	Cancers studied		Percentage of patients
		n	Percentage	
Male	Basal cell carcinoma	13	52%	65%
	Squamous cell carcinoma	11	44%	55%
	Bowens disease	1	4%	5%
	Total	**25**	**100%**	**125%**
Female	Basal cell carcinoma	19	54%	63%
	Squamous cell carcinoma	15	43%	50%
	Bowens disease	1	3%	3%
	Total	**35**	**100%**	**117%**

Table 2.5 shows the percentage of the type of cancer according to gender.

A total of 32 patients had basal cell carcinomas, 13 were male and 19 were female.

A total of 26 patients had squamous cell carcinomas, 11 were male and 15 were female.

A total of 2 patients had Bowens disease, 1 was male and 1 female.

From the 25 male patients studied, the results are presented in table 2.5 as follows:

13 (65%), male patients had basal cell carcinoma, 11 (55%) male patients had squamous cell carcinoma and 1 (5%) male patient had Bowens disease.

From the 35 female patients studied, the results are presented in table 2.5 as follows:

19 (63%), patients had basal cell carcinoma, 15 (50%) had squamous cell carcinoma and 1 (3%) had Bowens disease.

Table 2.6: Type of cancer by Age group

Age group	**Type of Cancer**	**Cancers studied**		**Percentage of patients**
		n	**Percentage**	
18 - 30 years	Basal cell carcinoma	5	71%	83%
	Squamous cell carcinoma	2	29%	33%
	Total	**7**	**100%**	**117%**
31 - 40 years	Basal cell carcinoma	11	46%	61%
	Squamous cell carcinoma	13	54%	72%
	Total	**24**	**100%**	**133%**
41 - 50 years	Basal cell carcinoma	5	63%	63%
	Squamous cell carcinoma	3	38%	38%
	Total	**8**	**100%**	**100%**
51 - 60	Basal cell carcinoma	4	44%	50%
	Squamous cell carcinoma	4	44%	50%
	Bowens disease	1	11%	13%
	Total	**9**	**100%**	**113%**
>60 years	Basal cell carcinoma	7	58%	70%
	Squamous cell carcinoma	4	33%	40%
	Bowens disease	1	8%	10%
	Total	**12**	**100%**	**120%**

Table 2.6 shows the percentage of the type of cancer according to the patients' age group.

A total of 32 patients had Basal cell carcinoma, 5 were 18-30 years old, 11 were 31-40 years old, 5 were 41-50 years old, 4 were 51-60 years old and 7 were more than 60 years old.

A total of 26 patients had Squamous cell carcinoma, 2 were 18-30 years old, 13 were 31-40 years old, 3 were 41-50 years old, 4 were 51-60 years old and 4 were more than 60 years old.

A total of 2 patients had Bowens disease, 1 was 51-60 years old and 1 was more than 60 years old.

For the 18-30 year old group, 7 patients were studied. The results are presented in table 2.6 as follows: 5 (83%) patients had BCCs and 2(33%) patients had SCCs.

For the 31-40 year old group, 24 patients were studied, 11 patients of which had BCCs (61%) and 13 (72%) patients had SCCs.

For the 41-50 year old group, 8 patients were studied, out the 8 patients 5 (63%) patients had BCCs and 3 (38%) had SCCs

For the 51-60 year old group, 9 patients were studied and 4 (50%) had BCCs, 4 (50%) had SCCs and 1 (13%) had Bowens disease.

For the 60+ year old group, 12 patients were studied, 7 (70%) patients had BCCs 4 (40%) had SCCs and 1 (10%) had Bowens disease.

Table 2.7: Type of cancer by Site of skin cancer

Type of cancer	Site of skin cancer	Cancers studied		Percentage of patients
		n	**Percentage**	
Basal cell carcinoma	Head and neck	20	69%	83%
	Upper extremities	3	10%	13%
	Lower extremities	4	14%	17%
	Trunk	1	3%	4%
	Unspecified	1	3%	4%
	Total	**29**	**100%**	**121%**
Squamous cell carcinoma	Head and neck	11	48%	52%
	Upper extremities	4	17%	19%
	Lower extremities	6	26%	29%
	Unspecified	2	9%	10%
	Total	**23**	**100%**	**110%**
Bowens disease	Lower extremities	2	100%	100%

Table 2.7 indicates that for patients with Basal cell carcinoma the site of the cancer was as follows; 20 (83%) was on the head and neck region, 3 (13%) on upper extremities, 4 (17%) on lower extremities, 1 (4%) on the trunk and 1 (4%) was on unspecified sites.

It also indicates that for patients with Squamous cell carcinoma the commonest site of the cancer was the head and neck region with 11 (52%), 4 (19%) was on upper extremities, 6 (29%) on lower extremities and 2 (10%) were on unspecified sites.

The results also indicate that for patients with Bowens disease, both cases were located in the lower extremities (100%)

Table 2.8: BCC by Gender

Gender	BCC	Frequency	Percentage
Male	Basosquamous cell	4	36%
	Nodular	4	36%
	Superficial	1	9%
	Unspecified	2	18%
	Total	**11**	**100%**
Female	Basosquamous cell	1	7%
	Micronodular	1	7%
	Morpheaform	1	7%
	Nodular	6	43%
	Superficial	5	36%
	Total	**14**	**100%**

Table 2.8 indicates that there were 25 patients with BCC. The sample had 11 males and 14 females. For the male patients, 4 (36%) had Basosquamous cell, 4 (36%) had Nodular, 1 (9%) had Superficial and 2 (18%) has unspecified BCC.

For the female patients, 1 (7%) had Basosquamous cell, 1 (7%) had Micronodular, 1 (7%) had Morpheaform, 6 (43%) had Nodular, 5 (36%) had Superficial.

Table 2.9: BCC by Site of skin cancer

BCC		Cancers studied		Percentage of patients
		n	**Percentage**	
Basosquamous cell	Head and neck	5	100%	100%
	Total	**5**	**100%**	**100%**
Micronodular	Upper extremities	1	100%	100%
	Total	**1**	**100%**	**100%**
Morpheaform	Head and neck	1	100%	100%
	Total	**1**	**100%**	**100%**
Nodular	Head and neck	9	90%	90%
	Lower extremities	1	10%	10%
	Total	**10**	**100%**	**100%**
Superficial	Head and neck	5	45%	83%
	Upper extremities	1	9%	17%
	Lower extremities	3	27%	50%
	Trunk	1	9%	17%
	Unspecified	1	9%	17%
	Total	**11**	**100%**	**183%**
Unspecified	Upper extremities	1	50%	50%
	Lower extremities	1	50%	50%
	Total	**2**	**100%**	**100%**

The sample had 30 selections for BCC. From the sample of 30, 5 (17%) had basosquamous cell, 1 (3%) had micronodular, 1 (3%) had morpheaform, 10 (33%) had Nodular, 11 (37%) had Superficial and 2 (7%) had unspecified BCC.

For the patients with basosquamous cell, 5 (100%) had the cancer located in the head and neck region.

The patient with micronoduar BCC had the cancer located in the upper extremities.

The patient with morpheaform BCC had the cancer located in the head and neck.

The 10 patients with nodular BCCs, 9 (90%) had the cancer located in the head and neck region; and 1 (10%) in the lower extremities.

For the 11 patients with Superficial BCCs, 5 (83%) had the cancer on the head and neck, 1 (17%) in the upper extremities, 3 (50%) in the lower extremities, 1 (17%) on the trunk and 1 (17%) on unspecified sites.

There were two patients with unspecified BCCs, 1 (50%) was located in the upper extremities and the other in the lower extremities.

Table 2.10: SCC by Gender

Gender	SCC	Frequency	Percentage
Male	Poorly differentiated	3	33%
	Moderately differentiated	1	11%
	Well differentiated	3	33%
	Unspecified	2	22%
	Total	**9**	**100%**
Female	Poorly differentiated	4	33%
	Moderately differentiated	3	25%
	Well differentiated	5	42%
	Total	**12**	**100%**

Table 2.10 indicates that there were 21 patients with SCC. The sample had 9 males and 12 females. For the male patients, 3 (33%) were poorly differentiated, 1 (11%) were moderately differentiated, 3 (33%) were well differentiated and 2 (22%) had unspecified SCC.

For the female patients, 4 (33%) were poorly differentiated, 3 (25%) moderately differentiated, 5 (42%) were well differentiated.

Table 2.11: SCC by Site of skin cancer

SCC		Cancers studied		Percentage of patients
		n	**Percentage**	
Poorly differentiated	Head and neck	4	57%	57%
	Upper extremities	1	14%	14%
	Unspecified	2	29%	29%
	Total	**7**	**100%**	**100%**
Moderately differentiated	Head and neck	3	60%	75%
	Lower extremities	2	40%	50%
	Total	**5**	**100%**	**125%**
Well differentiated	Head and neck	4	44%	50%
	Upper extremities	3	33%	38%
	Lower extremities	2	22%	25%
	Total	**9**	**100%**	**113%**
Unspecified	Lower extremities	2	100%	100%
	Total	**2**	**100%**	**100%**

The sample had 23 selections for SCC. From the sample of 23, 7 were poorly differentiated, 5 were moderately differentiated, 9 were well differentiated and 2 were unspecified.

From the poorly differentiated, 4 (57%) had the cancer located in the head and neck, 1 (14%) in the upper extremities and 2 (29%) in unspecified locations

From the moderately differentiated SCCs, 3 (75%) had the cancer on the head and neck region; 3 (38%) in the upper extremities and 2 (22%) in the lower extremities.

There were two patients who had unspecified SCC in both cases the cancer was located in the lower extremities.

DISCUSSION

In this retrospective study of Non melanoma skin cancers in patients with OCA at Chris Hani Baragwanath Academic Hospital, we report 50 patients with confirmed NMSCs on histopathology reports.

In this study there was a female predominance with 60% patients being female and 40% male. This is in not in keeping with Kiprono et al 10 year retrospective review in Tanzania where there was a male: female ratio of 1:1.(Kiprono et al., 2014) Emadi et al reported a slight male predominance in a study done in Kenya in 2017.(Emadi et al., 2017) However in the same study there was a significant female predominance in the pre malignant lesions. This is most likely linked to females paying more attention to the appearance of their skin and thus seeking medical advice earlier than males. The last South African study by Kromberg et al in 1989 did not report gender demographics.(Kromberg et al., 1989)

In the current study, the youngest patient was 19 years old and the oldest was 81 years old. The mean age was 45.44 year and the median age was 43 years from the sample of 50 patients. This is also not in keeping with Kiprono et al study in Tanzania which showed a mean age of 35 years. While previous studies in Nigeria and Tanzania reported a mean age of 30.(Mabula et al., 2012) With the same studies reporting that few albinos survive beyond 30 years. In the South African study by Kromberg et al, 31% of the patients had skin lesions including cancers by the age 20 and 42% by the age 30. The higher mean age in our study could represent an increase in the survival rate which can be attributed to increased awareness, preventative measures and early treatment of pre malignant lesions as well as skin cancers. The difference in mean ages between our study and those done in Tanzania could be explained by the finding of previous studies in Nigeria and Tanzania that reported that albinos living closer to the equator have an increased risk of skin cancers. These group of albinos develop sun damage,

premalignant lesions and malignant tumors by the age of 20 with few albinos surviving beyond age 30.

Our study showed a higher percentage of BCCs then SCCs and a low rate of bowens disease. Amongst the 50 patients studied, 36 had BCCs, 26 SCCs and 2 had bowens disease. 7 out of the 50 patients had both BCCs and SCC at different sites of the body with one patient having all 3 at different sites. Emadi et al in a prospective study in Kenya, there was a BCC predominance (60%) and SCC (30%). However this was a small sample size study with only 20 patients with NMSCs. Our study is in contrast to Kiprono et al study as well as other studies done in Nigeria and Tanzania, which showed a slight SCC predominance. In the Kiprono et al study the ratio of SCC: BCC was 1.2:1.(Mabula et al., 2012, Kiprono et al., 2014)

The development of SCC is associated with a high cumulative dose of UVR, with the maximum incidence closest to the equator, as the incidence doubles with every 8-10 degree decrease in latitude, which could explain the contrast in our studies and those done in Nigeria and Tanzania.(Mabula et al., 2012) BCCs were predominant in all the age groups with the highest percentage between the ages 31 – 40 (32%). Out of the 26 patients with SCCs, 50% were between the ages of 31 – 40. This is in keeping with the Kiprono et al study where the age of majority of their patients was between 20 – 45 years. It is also in keeping with the South African study by Kromberg et al where 42% had cancers by end of third decade.

NMSCs tend to occur on sun exposed areas with the head and neck region being the commonest site. In our study BCCs were more common in the head and neck region (69%), upper extremities (10%), lower extremities (4%) and trunk (3%). 1 patient (3%) had an unspecified site. When compared to other studies in Africa the head and neck region remains the commonest site for BCCs.

In the SCC group, the head and neck region (48%) was also predominant. The upper extremities (17%), lower extremities (26%) and 2 (9%) had unspecified site. Our findings are supported by Opera et al study in Eastern Nigeria and Tanzania which reported that SCC was mostly found in the head and neck region. Emid et al study also showed similar findings.(Emadi et al., 2017) The 3 patients with Bowens disease were both in the lower extremities. There are no studies that reported Bowens disease in albinos. It could be that these were grouped under SCCs in some studies. Bowens disease is a squamous cell carcinoma in situ. Its development has been linked to UVR exposure as well as arsenic exposure and HPV infections. The lesions may appear anywhere on the body, a scaly sharply demarcated plaque which could easily be misdiagnosed as psoriasis. It is therefore possible that the lesions of Bowens were missed in previous studies.

The study revealed a female predominance in both types of skin cancers, which is in keeping with the overall demographic finding of the study. Amongst the BCCs group, 44% was males and 56% females. In the SCC group, females made up 57% and males 43%.

The commonest histological subtype of BCCs is the nodular type. This is also reflected in our study. 34 of the 50 patients had BCCs, 13 of those had the nodular type (40.6%), followed by 9 patients with the superficial type (28.1%), 9 had the basosquamous type (15.6%), 3 had the morphaeform (9.4%) and 2 had the micronodular type (6.3%). 2 patients had an unspecified subtype. Males had more nodular and basosquanous types compared to the females who had more nodular and superficial type.

These findings are in keeping with the Tanzanian study that showed a predominance of the nodular type but in that study the morpheaform was the second commonest followed by the superficial.(Kiprono et al., 2014) The author then concluded that albinos are more predisposed to the more aggressive type of BCC when compared to their Caucasian

counterparts. The nodular type was most common in the head and neck region, with 90% on the head and neck and 10% on lower extremities. All the basosquamous and morpheaform (100%) subtypes were found in the head and neck region. The micronodular type was in the upper extremities. The superficial BCCs were more widely distributed with 45% in the head and neck, 27% on lower extremities, 9% on the trunk and 9% on upper extremities. There are no previous studies that have compared this subtype by location.

SCCs are classified as either well, moderately or poorly differentiated histologically. Out of our 50 patients, 27 had SCCs. In this study there was a predominance of the well differentiated subtype (33.3%), followed by the poorly differentiated (29.6%) and moderately differentiated at (18.5%). 18.5% of SCC were not specified. These findings are similar to those in the Tanzanian study where 50%of the SCCs were well differentiated. However, in that study the well differentiated was closely followed by moderately differentiated (43.1%) and poorly differentiated (6.9%).

Amongst the male patients the rate of well differentiated and poorly differentiated was equal (33%) and moderately differentiated (11%). The rest were not specified. Amongst the female patients, well differentiated were predominant (42%), followed by poorly differentiated (33%) and moderately differentiated (25%). Overall, the SCCs were predominantly located in the head and neck region. 57% of the poorly differentiated were found on the head and neck, 60% of the moderately differentiated and 44% of the poorly differentiated. These are similar to the Kenyan study by Emadi et al that showed the head and neck region as the commonest site for SCCs as well as pre malignant lesions like actinic keratosis.

Some of the limitations in this study was the fact that some clinical data was missing on some of the lab reports such as whether the patient is an albino leading to exclusion of these patients from the study, which made the sample size smaller. However, this is the largest study to be done in Johannesburg since the last similar study by Kromberg et al. in 1989. In

some of the reports, other comorbidities like HIV or any organ transplant history were not included. Therefore the comorbidities on the data collection sheet could not be studied and thus not reported. The site and subtype of the lesions were also not specified in some of our reports. Some results were inconclusive of malignancy due to sampling error and inadequacy of the biopsies.

CONCLUSION

Non melanoma skin cancers are overwhelmingly predominant in albinos. Basal cell carcinomas are predominant over squamous cell carcinomas in South Africa. This is the first study in Johannesburg to describe the prevalence of histologically confirmed skin cancers in this population group. More studies still need to be done to describe the exact prevalence in South Africa and Africa particularly in regions closer to the equator where albinos are most at risk of cancer development.

More awareness and patient education is needed on sun protection and sun avoidance. It is important for clinicians to be able to detect and treat pre malignant lesions to prevent these serious sequelae.

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CHAPTER 3

APPENDICES

DATA COLLECTION SHEET

DEMOGRAPHIC INFORMATION	
1. Age of patient	1. Male
2. Sex	3. Female
	4. Unknown

TYPES OF SKIN CANCER	
1. Basal cell carcinoma	1. Yes 2. No
2. Squamous cell carcinoma	1. Yes 2. No
3. Bowens disease	1. Yes 2. No
4. Other	1. Yes 2. No
SITE OF SKIN CANCER	
1. Head and neck	1. Yes 2. No
2. Upper extremities	1. Yes 2. No
3. Lower extremities	1. Yes 2. No
4. Trunk	1. Yes 2. No
5. Other sites	1. Yes 2. No
6. Not specified	
HISTOLOGIC SUBTYPES	
1. BCC	E.g. Superficial, nodular, cystic, etc.
2. SCC	E.g. Well differentiated, poorly differentiated, etc.
OTHER FACTORS	
1. HIV infection	1. Yes 2. No 3. Unknown
2. Other immune suppression (organ transplant)	1. Yes 2. No 3. Unknown

ETHICS CLEARANCE

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr SO Buthelezi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M190448

NAME: (Principal Investigator)	Dr SO Buthelezi
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Dermatology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	A descriptive retrospective study of non-melanoma skin cancers in African patients with albinism at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	2019/04/26
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor E Ndobe & Dr SA Sibisi
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2019/06/06

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 on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

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 submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in April and will therefore reports and re-certification will be due early in the month of April each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES