CLINICOPATHOLOGICAL SPECTRUM OF CUTANEOUS MALIGNANCIES AT THE SKIN TUMOUR CLINIC, CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL IN JOHANNESBURG, SOUTH AFRICA: A 5-YEAR RETROSPECTIVE REVIEW.

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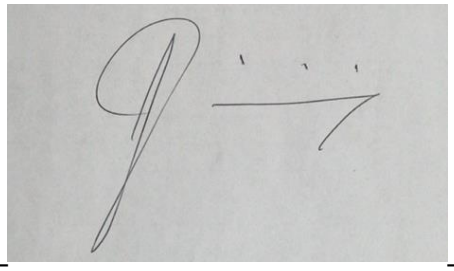
(1872655)

A research report (in the format of a “submissible” paper) 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 (Dermatology).

Johannesburg, July 2023.

DECLARATION

I, **Tapiwa Gwinji**, declare that this research report (in the format of a "submissible" paper) is my own, unaided work. It is being submitted for the Degree of Master of Medicine (Dermatology) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



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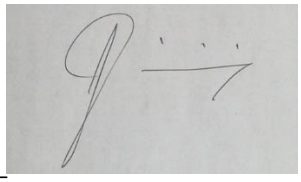
July 2023 in Johannesburg

CONTRIBUTION OF THE CANDIDATE TO THE PAPER

Declaration: Student's contribution to article(s) and agreement of co-author(s)

I, Tapiwa Gwinji, student number 1872655, declare that this Research Report is my own work and that I contributed significantly towards research findings presented in the paper intended for publication below.

Signature of Student _____ 

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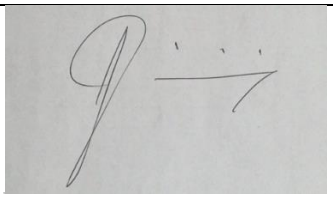
1st author	Tapiwa Gwinji		July 2023
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ABSTRACT

Background

Skin cancer is the most common malignancy in South Africa, incidence of which continues to rise. This disease remains a consistent problem in South Africa due to a multifactorial risk complex arising mainly from the high levels of year-round Ultraviolet (UV) exposure, high burden of HIV and late health seeking behaviour leading to poly-etiological skin cancers. Despite the ever-present danger that is cancer, the data and literature surrounding skin cancers among different races and ethnic groups remains inadequate as there are few population-based cancer registries in South Africa and only histologically confirmed cancers are logged into the national cancer registry.

Objectives

To describe the nature, extent and demographic characteristics of patients with histologically confirmed skin cancer seen at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) multidisciplinary skin cancer clinic during the period of January 2015 to December 2019 and to add to the body of literature concerning skin cancers in South Africa.

Methods

A retrospective chart review identified all patients who were managed for histologically confirmed malignant skin tumours at CMJAH skin tumour clinic. Types, quantity and distribution of common invasive malignancies by population group, age, gender, anatomical site and risk factor were explored.

Result

A total number of 531 participants with histologically confirmed skin cancers were identified. The most common malignancies were Kaposi's sarcoma(KS) (53.2%), squamous cell carcinoma (SCC) (27.0%), basal cell carcinoma (BCC) (10.4%), cutaneous melanoma (CM) (7.4%) and mycosis fungoides (MF) (4.2%). SCC and AIDS-associated KS were the most common skin cancer in the white and black population respectively.

Conclusion

This study provides valuable scientific data on the distribution and patient demographics of skin cancer in the public health system in Johannesburg, South Africa, on which further research can be based. This study highlights the burden of HIV associated skin cancer in this region. There is a need for further research and equitable appropriation of resources and public health awareness efforts towards strengthening UV and HIV-related skin cancer prevention initiatives in SA.

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AIDS Acquired Immune-Deficiency Syndrome

ALM Acral Lentiginous Melanoma

BCC Basal Cell Carcinoma

CM Cutaneous Melanoma

CMJAH Charlotte Maxeke Johannesburg Academic Hospital

DFSP Dermatofibrosarcoma Protuberans

HAART Highly Active Anti-Retroviral Therapy

HHV8 Human Herpes Virus 8

HIV Human Immunodeficiency Virus

KS Kaposi's Sarcoma

MF Mycosis Fungoides

NCR National Cancer Registry

NMSC Non-Melanoma Skin Cancer

OTR Organ Transplant Recepient

RT Radiotherapy

SCC Squamous Cell carcinoma

UV Ultra-Violet

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INTRODUCTION

Skin cancers are the 4th most commonly diagnosed type of cancer globally[1,2]and the most diagnosed cancer in South Africa[3]. The incidence of skin cancer continues to rise yearly throughout the world.

The epidemiology of skin cancers is South Africa is not well understood largely due to the lack of adequate numbers of population based cancer registries[4] as well integrated national cancer surveillance networks.[5,6] This makes it difficult to assess if trends in the South African cancer burden are following global patterns.

The prevalence of these cancers varies across all races. South Africa is home to a diverse multi-ethnic population of 59 million people.[7] 79.4% of South Africans are registered as Black, 9.2% as White, 8.8% as Coloured (non-derogatory term in South Africa meaning of mixed black and white race) and 2.6% are registered as Asian (of Asian or Indian descent). Skin cancers occur in all racial and ethnic groups in the country, with the the most commonly reported being SCCs, BCCs, KS and Cutaneous Melanoma (CM), in that order.[6,8–11]

As a result of a multifactorial risk complex, skin cancers are a growing problem in South Africa. These risk factors include high levels of year-round UV-radiation exposure, a high burden of HIV in the population, immunosuppressive and genetic diseases that predispose to skin cancer as well as a variety of other environmental and phenotypic factors present in the population.[12,13,14]

Due to its geographical location, South Africa experiences more than 2500 hours of sunshine a year in most regions.[15,16] In summer months this sunshine correlates to high levels of Ultra-violet radiation exceeding 10 on the UV index.[15] This high level of UV radiation and increased occupational and recreational exposure to sunlight places the population at high risk of skin cancer.[13,17] The country also has the highest number of people living with HIV in

the world.[18,19] These individuals have nearly 3 times the risk of developing skin cancers compared to HIV negative individuals.[20–25] While the risk of AIDS-defining cancers has declined since the advent of the HAART era, the incidence of non-AIDS defining cancers has increased, leading to a shift in the spectrum of cancers in people with HIV.[20,21]

Despite the growing incidence of skin cancers worldwide[26,27] research data in developing countries, including South Africa, on the spectrum of skin cancers are limited, with most studies being conducted in countries with predominantly white populations.[28] There is need for more data on skin cancer demographics and associated risk factors in South Africa, which will contribute to the development of a context specific skin cancer registry to inform disease management, resource allocation and cancer prevention strategies.

AIMS AND OBJECTIVES

The aim of this research was to assess the clinicopathological spectrum of histologically confirmed cutaneous malignancies presenting the CMJAH Skin Tumour Clinic over a 5-year period from January 2015 to December 2019

In addition, we documented the demographics of patients who attended the Skin Tumour Clinic over this 5-year period.

We also sought to outline and assess the skin cancer risk factors shown by the patients who attended the Skin Tumour Clinic and determine if this skin cancer burden follows global patterns.

MATERIALS AND METHODS

Study population

A retrospective record review of all patients who presented with a histopathologically confirmed primary skin cancer diagnosis, who presented to the skin tumour clinic at CMJAH from January 2015 to December 2019. Diagnosis was determined by histological analysis of skin punch or skin excision biopsies. Excluded from the study population were patients without demographic data, histologically confirmed diagnoses of skin cancer and patients with secondary skin cancers due to metastases from internal malignancies.

Study Setting

The skin tumor clinic is a once-weekly multi-disciplinary clinic run by Radiation-oncologists and Dermatologists. Patients are referred from Tertiary level hospitals as well as specialist clinics from Quaternary hospital units in Gauteng. All attendees to clinic have patient file containing demographic, clinical and treatment information. These files are stored in a record room adjacent to clinic in alphabetical order as per surname and 1st name. Patient names were collected from patient register of tumor clinic attendees during study period and files manually extracted. 538 files were retrieved. 7 files were excluded due to lack of demographic or histological data or illegibility due to water damage.

Data Collection.

A retrospective patient chart review of histologically confirmed new primary cutaneous malignancies that presented to the Skin Tumour clinic at CMJAH from 1 January 2015 to 31 December 2019 was conducted. Data was manually extracted from patient records using a data collection sheet and presented on an excel spreadsheet which tabulated demographic information such as age, patient gender and ethnicity; Clinical information such as type and anatomical location of skin tumour; Risk factors for skin cancer documented by managing clinicians including HIV status and immunological status where applicable were also captured as well as treatment modality offered and outcomes of management. Names of the patients were not recorded and patient identity was in the form of unique identifier numbers.

Statistical analysis

A data capture sheet was used to keep study records which were then transcribed onto an excel spreadsheet. Data was then imported to STATA (12.1) and all analyses were conducted using STATA (12.1). Descriptive statistics were calculated and reported. Microsoft Excel was used to produce graphs. Percentages were used to report categorical data.

RESULTS

Demographic characteristics

A total of 531 patients were recruited into the study. The patients were grouped into categories according to their ethnicities. Ethnic groups were Asian, Black, Coloured and White.

73.26%(n = 389) of all patients identified as black, 25.24%(n = 134) identified as white, 1.13%(n = 6) identified as coloured and 0.38%(n = 2) as Asian.

57.4% of study participants were male (n = 305) and 42.6% were female (n = 226). The mean age of presenting patients was 48 years of age. Age of the study population ranged from 15 to 97 years of age. Standard deviation was 16.2.

51.79% of the study population was between 30-49 years of age at presentation.

The 40-49 years age group had the highest number of patients with 26.04% (n=138) of which 36% (n=49) were female and 64% (n=89) were males. The second highest age group was the 30-39 age group with 25.85% (n=137) of the patients in this age group of which 47% (n=64) were female and 53% (n=73) were male (Table 1).

Age group in years	Total n (%)	Female n (%)	Male n (%)
0-19	5 (0.94)	3 (60)	2 (40)
20-29	38 (7.17)	23 (61)	15 (39)
30-39	137 (25.85)	64 (47)	73 (53)
40-49	138 (26.04)	49 (36)	89 (64)
50-59	77 (14.53)	28 (36)	49 (64)
60-69	66 (12.45)	23 (35)	43 (65)
70-79	47 (8.87)	22 (47)	25 (53)
≥80	22 (4.15)	14 (64)	8 (36)

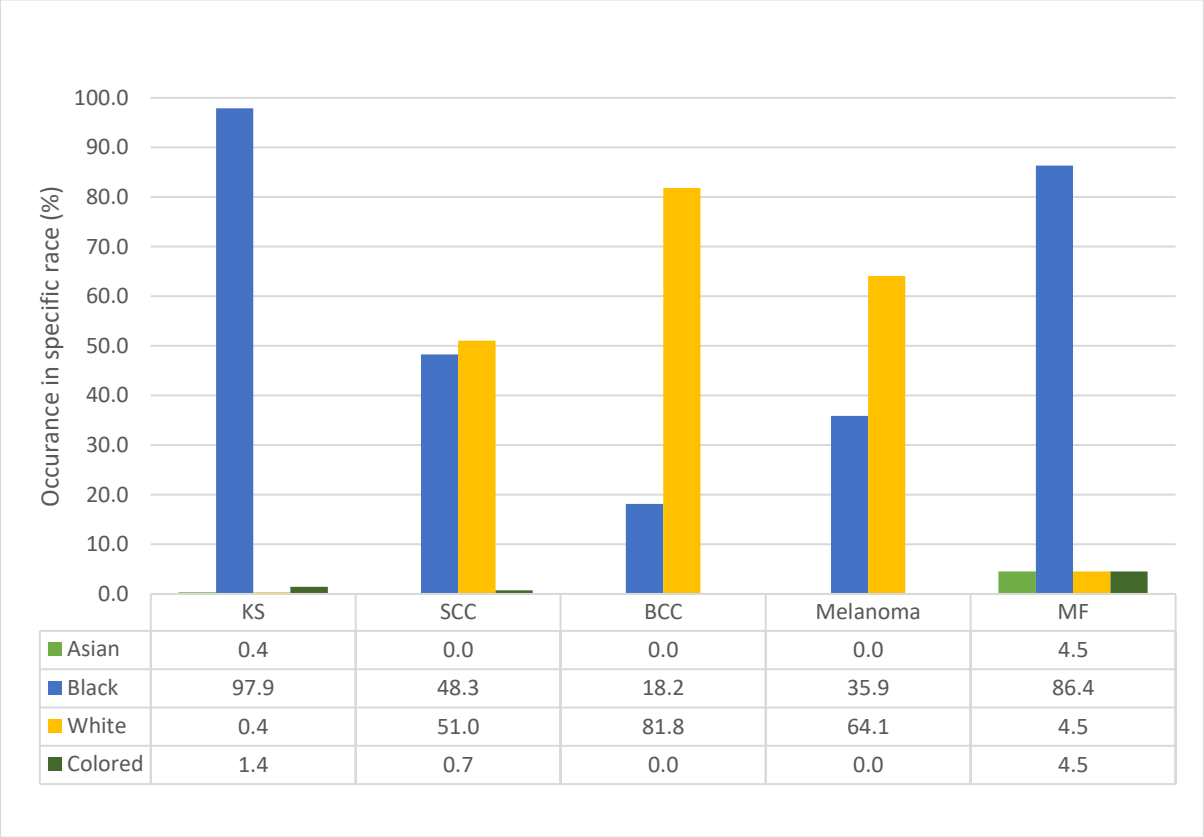
Table 1. Distribution by age category of male and female patients in study population.

Histopathological distribution of cancers

The 5 most common cancers seen were KS (most common, representing 53.2%), SCC, BCC, CM and MF in that order. The remaining types had an incidence of less than 1% showing that they were not common. (Table 2)

Skin Cancer types	n (%)
KS	282 (53.2)
SCC	143 (27.0)
BCC	55(10.4)
Cutaneous Melanoma	39 (7.4)
MF	22 (4.2)
Merkel Cell Carcinoma	2 (0.4)
DFSP	1 (0.2)
Porocarcinoma	1 (0.2)
Spindle cell neoplasm	2 (0.4)

Table 2. Histopathological distribution of skin cancers in study population.



	KS	SCC	BCC	Melanoma	MF
Asian	0.4	0.0	0.0	0.0	4.5
Black	97.9	48.3	18.2	35.9	86.4
White	0.4	51.0	81.8	64.1	4.5
Colored	1.4	0.7	0.0	0.0	4.5

Figure 1. Skin cancer distribution by population group.

The race-specific breakdown of these cancers is seen in Figure 1. The highest occurrences of KS and MF was in black people with 97.9% (n=276. The highest occurrences of SCC, CM and BCC were in the White cohort. Of the 530 patients, 4% (n=22) had MF. There was an insignificant occurrence of the other remaining cancers with a percentage value less than 1%.

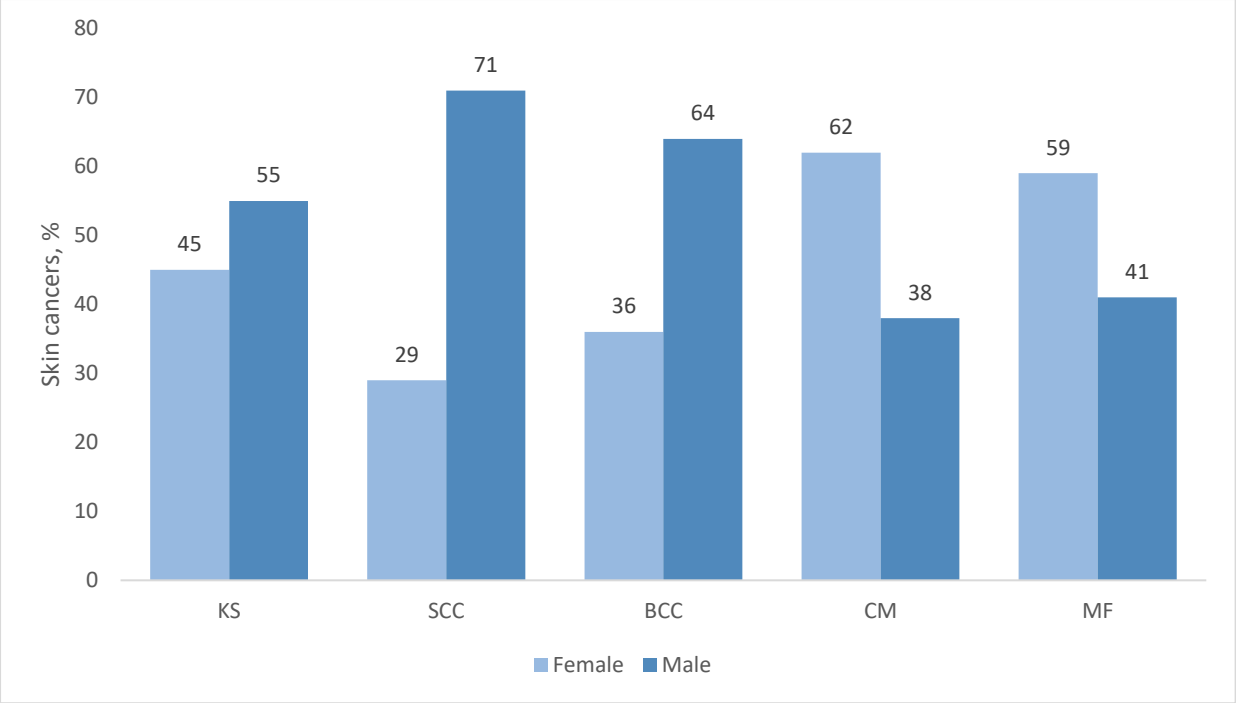


Figure 2. Skin cancer distribution by gender.

Figure 2 shows cancer distribution by gender. Males were more affected by KS, SCC and BCC. Melanoma and MF occurred more commonly in females as compared to males.

Table 3 showed anatomic prevalence of common skin cancers in the different ethnic groups of our study population.

CANCER TYPE & RACE	Lesion Location				
	Head and Neck	Trunk	Limbs	Orolabial	Anogenital
KS					
Black	12.0	10.1	70.7	6.1	1.1
White	0	0	100	0	0
Coloured	0	0	50	50	0
Asian	0	0	100	0	0
SCC					
Black	24.6	10.1	21.7	0	43.5
White	75.3	8.5	15.1	0	4.1
Coloured	0	100	0	0	0
Asian	0	0	0	0	0
BCC					
Black	89.0	11	0	0	0
White	88.4	4.6	7.0	0	0
Coloured	0	0	0	0	0
Asian	0	0	0	0	0
CM					
Black	7.2	0	92.8	0	0
White	20	36.0	39.9	0	4.1
Coloured	0	0	0	0	0
Asian	0	0	0	0	0
MF					
Black	5.6	94.4	0	0	0
White	0	0	100	0	0
Coloured	0	0	50	50	0
Asian	0	0	100	0	

Table 3. Anatomical Distribution of cancers in ethnic groups.

Treatment	Frequency	Percentage (%)
Nil Offered	98	18.45
Chemotherapy	17	3.20
Radiotherapy	291	54.80
Chemotherapy + Radiotherapy	44	8.29
Surgical excision	51	9.60
HAART	22	4.14
Other	8	1.57

Table 4. Distribution of skin cancer treatment modalities instituted in the study population

Table 4 shows treatment modalities that were instituted to manage skin cancers in the study population and their distribution. The most frequent treatment method used was Radiation therapy with 54.80% (n=291) of the patients receiving this treatment. 18.45% (n=98) of the study population received no treatment from the Skin Tumour clinic. 4.15% (n=22) previously naïve patients had HAART initiated as a treatment by the Skin Tumour clinic. All the other treatment methods were used with an individual frequency less than 1% showing that they were not so common. These included use of interferon, methotrexate, topical corticosteroids each used in 0.19%(n=1) of cases and NB-UVB and PUVA used in 0.56%(n=3) and 0.38%(n=2) of cases respectively.

Outcome	Number of patients (n)	Percentage (%)
Lost to follow-up	204	38.49
Deceased while under follow-up	12	2.26
Discharged to CMJAH medical oncology for further management	88	16.60
Discharged post treatment	21	3.96
Discharge to CMJAH dermatology for further management	25	4.72
Discharged to other unit/hospital	98	18.49
Discharged to CMJAH surgical department for further management	37	6.97
Not documented	5	0.94
Self-discharge	15	2.83
Still under follow up	26	4.91

Table 5. Management outcomes in study population.

Table 5 shows the management outcomes for the patients in the study. 38.49% (n = 204) were lost to follow-up and did not have their final outcomes documented within their patient records. 4.91% (n=26) were still under follow up at time of data extraction from their patient records. 2.83% (n=15) of the patients opted not to undergo treatment and self-discharged. 2.26% (n=12) of the patients died while under management and 1.32% (n=7) were discharged post treatment.

Risk Factor	SCC	BCC	KS	CM	MF
HIV	25.9	7.3	92.9	2.6	27.3
Sun exposure	39.2	58.2	0	41.0	0
Smoking	31.5	38.2	6.0	23.1	4.5
No documented Risk Factor	10.5	3.6	0	38.5	59.1
Family History of skin cancer	13.3	21.8	0	12.8	9.1
Albinism	7.7	12.7	0	0	0
Previous skin cancer	9.8	12.7	0.7	10.3	4.5
Prior history of Injury at cancer site	7.0	0	0	0	0

Table 6. Risk Factors found in skin cancers (%)

Commonest risk factor in SCC was sun exposure (39.2% n=56) and in BCC (58.2% n=32). Commonest risk factor for KS was HIV (92.9% n=262). Commonest risk factor for CM was sun exposure (41% n=16). Commonest risk factor for MF was HIV (27.3% n=6) (Table 5).

DISCUSSION

Our study enrolled 531 participants out of a total possible 538 patients. 7 patient records could not be located for analysis. The majority of the study population was Black (73.26%; n=389), 25.24% (n=134) were White, 1,13%(n=6) were Coloured (n=6) and 0.35%(n=2) were Asian. This predominance in Black participants correlates to the ethnic distribution of the Johannesburg population which is 76.4% Black.[29]

There was a low population of Coloured and Asian participants in our study, 1.13% and 0.35% respectively, relative to the population breakdown of Johannesburg of 5.6% Coloured and 4.9% Asian. This may be explained by higher levels of access to private healthcare in these ethnic groups[30] as well as lower prevalence of HIV and UV-radiation related cancers in both these ethnic groups compared to Black and White patients. White participants in the study group were 25.24% which is more than double their ethnic distribution in Johannesburg of 12.3% which highlights the prevalence and high skin cancer burden among this population group in South Africa.

The average age of patients in the study population at initial presentation was 48 years. This figure is lower than the average age of presentation in similar studies conducted in different provinces of South Africa in which mean age at presentation was above 60 years.[9–11,31]

This difference in average age may be explained by the high prevalence of HIV in our study population in which 58.4% of the study population was HIV positive. 39.2% was HIV negative and the status of 2.4% of our cohort was undocumented. HIV has been postulated to lower the age of incidence of HIV and non-HIV associated cancers.[32,33]

The average time from occurrence of skin cancer until presentation to our clinic was 25 months. A prospective study done in the Eastern Cape, South Africa found the commonest reasons for late presentation among skin cancer patients were attributed to reasons that

corresponded with denial, lack of realisation of the seriousness of the lesion, and being scared or embarrassed about what the doctor might find.[34]

57.4%(n=305) of our study population was male and 42.6% was female. This is in keeping with other findings in South African studies and other regional as well as international study findings.[1,9–11,28,31,35,36,37] When we analysed the distribution of skin cancer types by gender KS,SCC and BCC were more common in males compared to females. CM and MF affected females more frequently than males in our study population. The gender distribution of KS in our study population replicates findings from several studies worldwide.[38–43] These gender differences between sexes can be explained by physiological protective factors in women i.e. Beta HCG and menstrual cycle hormones such as Follicle-Stimulating Hormone and Luteinizing Hormone which reduce risk of KS development.[44] Men have also been found to have a higher seroprevalence of HHV8 infection than female patients with subsequent higher prevalence of AIDS-associated KS.[40,45] The gender distribution of BCC and SCC in our study population, which also skewered towards a male predominance, also correlated with results from other studies conducted in in South Africa and worldwide[1,8,9,46]

The gender distribution of CM in our study population was skewered towards female patients (61%, n=24) which differed from findings from previously conducted audits of NCR data here in South Africa.[6,8] However cancer registry audits in other regions of Southern Africa such as Namibia, Botswana and Swaziland had similar findings to our study.[8]

UV related skin cancers are thought to be more common in men than women given that males historically performed more outdoor labour than females and were also less likely to use sunscreen and employ other sun protective measures.[47,48]

MF was more common in females (59.1% n=13) than males in our study group and 95.5%(n=21) of cases occurred in Black patients. This was in keeping with the gender distribution of MF in Blacks and people of color.[49,50]

Risk factors for skin cancer seen in our study cohort matched those seen in literature[20,22,24,26,36,41,51–53]. We noted HIV as the main risk factor for KS in our cohort. Significant occupational or recreational sun exposure was the most common risk factor for SCCs and BCCs in the study population overall and in the White cohort. However when assessed by race, HIV was the most common risk factor for SCCs, occurring in 50.1%(n=35) of Black patients with SCC. 60%(n=6) of Black patients with BCCs had albinism as the significant risk factor. This is in keeping with literature findings that the main risk factor for BCC in all populations is UV light [35,46,52,54–56]

KS was the most common type of cancer occurring in 53.2% (n=282) of the study population, followed by SCC occurring in 27% (n=143) of the population. Histological subtype was unknown in 55.9% of SCCs. 31.5% were of moderately differentiated subtype, 7.7% were poorly differentiated and 4.9% were well differentiated. The significance of differentiation is contentious. Some studies have cited moderate or poor differentiation as a major risk factor for metastasis and poor prognostic outcomes.[57–59] Moderately and poorly differentiated SCC tend to be seen in patients who present late[60] which is consistent with findings in our cohort where patients presented, on average, 25 months after onset of skin cancer.

BCC occurred in 10.4% (n=55) of the patients. Melanoma was ranked fourth, occurring in 7.4% (n=39) of the patients, MF was ranked fifth, occurring in 4.2% (n=22) of the patients. All the other remaining types accounted for less than 1% of cancers seen in the study

population showing that they were not common. Data released by the National Cancer Registry in 2019 showed that BCC, SCC,CM and KS in that order were the most common skin cancers diagnosed in South Africa in 2019.[3] Given that our study setting was in a joint tumor clinic in a radiation oncology unit, tumorous malignancies that were likely to have poor cosmetic outcomes after surgery, or be responsive to radiotherapy (in order to stop tumour bleeding, tumour pain and to shrink tumour size) were referred while other skin cancers were seen in other units such as dermatology, surgery and medical oncology. Radiotherapy (RT) modality is usually indicated for patients with large or more aggressive skin tumours, and tumours located in craniofacial areas where surgery is often avoided.[61]

SCC, BCC, CM, KS and MF were the most common cancers in the White cohort of our study population. These results differed from national and international findings in which BCC,SCC and CM, in decreasing frequency, were the most common skin cancers found in White patients.[3,8] Again this may be attributed to the nature of our clinic.

In the Black study population KS, SCC, MF, CM and BCC were the most common cancers in descending order. These results were in keeping with provincial and national data published in South Africa[3,9,10,31] These findings are also similar to findings in other predominantly Black countries with a high burden of HIV.[8,62]

In the White cohort of our study population 88.4% and 75.3% of BCCs and SCCs, respectively, occurred in the head and neck area while only 20% of CM occurred on the head and neck. 36% of CM occurred on the trunk and 40% on the limbs. This site distribution of CM and NMSC in the White cohort was in keeping with known trends of UV-associated skin cancer distribution in Caucasians.[63–68]

48.3%(n=69) of all SCCs in our study population occurred in the Black cohort. In this cohort 24.6% of SCCs occurred in the head and neck region, 23.2% in the genital area, 21.7% on the limbs,20.2% in the anal region and 10.1% on the trunk. Our findings support findings in other studies done in African Americans and Sub-Saharan Africa, including South Africa, that found that SCCs in Black patients predominate on non sun-exposed areas. [13,54,69,70,71] SCCs have been noted to occur in the anus in up to 25% of cases[69,72] and a review of the Tanzanian Cancer registry found that genitals were the 3rd most affected site in Black patients[70]

Predisposing factors for SCC in Black people and other people of colour include burn scars(thermal and chemical), chronic leg ulcers, immunosuppression and chronic inflammation including Hidradenitis suppurativa, lupus vulgaris and discoid lupus erythematosus.[20,54,69,72,73] 7%(n=10) of all SCCs in our study cohort had history of a prior injury or lesion at the site of SCC occurrence.

17.3%(n=9) of all BCCs in our study population were diagnosed in the Black cohort. 88.9% (n=8) of these BCCs occurred in the head and neck area. Interestingly only 3 of the 9 Black patients with BCCs did not have albinism as a risk factor. All BCCs in these 3 patients occurred in the head and neck area. These findings correlate with other studies which showed BCCs in the head and neck area in 89% of Black patients.[72,74]

14 patients with Oculocutaneous albinism (OCA) were included in our study population. 92.9%(n=13) were Black and 7.1%(n=1) were White. NMSCs of the head and neck accounted for 64.2%(n=9) of the skin cancer location in these patients. Patients with OCA in Sub-Saharan Africa have 1000-fold greater risk of developing NMSC of sun-exposed skin cancers than the general population.[53,55,75–77]

35.9%(n=14) of CM in our study population occurred in Black patients. 92.9% of these melanomas occurred on the lower limbs. This reinforces existing evidence that UV radiation is not a significant risk factor in melanoma in Black populations.[54,69,72] A study conducted in South Africa similarly found that 97% of melanomas in Black South Africans occurred on the lower limbs.[78] Acro-lentiginous melanoma is the most common subtype of melanoma in Black patients and has been noted to occur in up to 90% of cases of melanoma in Black patients world over.[10,11,54,74,79,80]

Black patients accounted for 97.9%(n=276) of all KS cancers diagnosed in our study population. KS was also the most common skin cancer in Black populations in audits conducted in 2 other South African Provinces.[9,31]in our Black study cohort, AIDS-associated KS accounted for 92.9% of cases. 7.1%(n=21) were noted to be of the endemic variant of KS. Previous studies in South Africa also noted a low prevalence of endemic KS in South Africa.[81,82,83] 70.1% of KS cases in the Black cohort occurred on the limbs and 6.1% of all cutaneous KS cases had concomitant palatal KS. This distribution of KS is similar to findings in other KS studies conducted in Black populations in Africa.[84]

Mycosis Fungoides is a chronic cutaneous T-cell lymphoma that is more common in Black patients compared to White patients.[49,50] The disease occurs more commonly on the trunk in women.[85,86] In our cohort 86.4% (n=18) of MF cases occurred in Black patients. The trunk was the predominantly affected region, thus our study found these observations to be true.

Radiation therapy was the primary treatment modality offered to patients in the study population (54.8% n=291). It was offered with either a curative or palliative intent in these patients. No cancer-related treatment was offered in 18.45% of patients(n=98). These were patients who typically presented with late-stage malignancy and were offered palliative hospice referral and supportive management. HAART was offered as the sole treatment to 4.1%(n=22) of our study population. All patients who were commenced on HAART in the study cohort had AIDS-associated KS and were previously ART naïve. HAART alone has been shown to effectively treat AIDS-associated KS in 40% of patients.[87] In South Africa as well as the rest of the continent, with high prevalence of HIV and HHV8, HAART as sole therapy provides important benefits in patients with AIDS-associated KS and should be used where possible, particularly in resource limited settings.[82,87,88] In our clinic the majority of KS patients presented with generalized, nodular or fungating KS. This necessitated the use of radiation in most of our KS cohort. The average duration of follow-up in our clinic was 9 months and 2 weeks.

38.5%(n=204) of patients in our study cohort were lost to follow-up, either after index presentation or during treatment. Similarly high levels of patient attrition have been noted in other oncology clinics in resource limited settings worldwide.[89–91] Reasons postulated have included adherence to harmful socio-cultural practices, fear of radiation treatment, lack of financial capacity of patients to meet costs of radiation therapy including daily travel and in some settings lack of access to oncology clinics. These factors need to be further studied to improve patient adherence and outcomes.

28.29%(n=150) of patients were discharged to other units at CMJAH for further management. These patients received adjuvant radiation to manage painful tumors, control

bleeding in tumors, shrink tumors prior to surgical resection and for palliative care. 18.11%(n=96) were discharged back to referring hospitals for further management after treatment.

Study Limitations

The retrospective, single-clinic nature of our study with the associated selection bias as well as the heterogenicity of our study population restricts the strength of our study. A multi-centre prospective study in South Africa would overcome this challenge.

There was no documentation of Fitzpatrick skin type without which we were unable to deduce the prevalence of UV-related malignancies in different skin types. Sun exposure documented as a risk factor in our study was subjective.

CONCLUSION

This study highlights the burden of HIV-associated and UV-related skin cancers presenting to a tertiary hospital clinic in Johannesburg, South Africa. There is need for equitable mobilisation of resources towards developing preventative initiatives tailored to the South African context to decrease incidence and morbidity of these cancers.

Late presentation of skin cancer patients leads to increased morbidity and financial cost to treat these patients. Population education campaigns on preventative measures and benefits of early health-seeking behaviour would see a decrease in morbidity of skin cancers.

There is need to examine the high levels of patient loss to follow-up at this and other oncology clinics and provide state-assisted social support to mitigate against patient loss where possible. We call for integrated population-based cancer registries to increase accuracy of databases and to assist in further research.

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APPENDIX A. APPROVED RESEARCH PROTOCOL WITH APPENDICES

CANDIDATE'S SURNAME: **GWINJI** [Please print]	FIRST NAME/S: **TAPIWA**	STUDENT NUMBER: **1872655**

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

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Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

03 January 2022
Person No: 1872655
PAG

Dr TM Gwinji

Dear Dr Tapiwa Gwinji

Master of Medicine in Dermatology: Approval of Title

We have pleasure in advising that your proposal entitled *Clinicopathological spectrum of cutaneous malignancies at the skin tumour clinic, Charlotte Maxeke Johannesburg Academic hospital in Johannesburg, South Africa: a 5-year retrospective review*. has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

CURRENT QUALIFICATIONS: **MD MSc**			
TEL: n/a	CELL: **0615337114**	E-MAIL: **tmgwinji@gmail.com**	FAX:n/a
DEGREE FOR WHICH PROTOCOL IS BEING SUBMITTED: **MMed in Dermatology**			
PART-TIME OR FULL-TIME: **FULL-TIME**			
FIRST REGISTERED FOR THIS DEGREE:	TERM : **1**	YEAR: **2020**	
DEPARTMENT: **MEDICINE (DERMATOLOGY)**			
TITLE OF PROPOSED RESEARCH: **Clinicopathological spectrum of cutaneous malignancies at a skin tumour clinic in Johannesburg, South Africa: A 5-year retrospective review.**			
CANDIDATE'S SIGNATURE:		DATE:**27/07/2021**	
SUPERVISOR 1 (NAME & SURNAME): **PROF DEEPAK MODI**		% Supervision **100**	
SUPERVISOR'S QUALIFICATIONS: **MBChB (WITS);DTM&H (RCP); MSc(LON); FC DERM (SA); FRCP**			
SUPERVISOR'S DEPARTMENT: **DERMATOLOGY**			
SUPERVISOR'S ADDRESS / TEL / E-MAIL: **CMJAH, JUBILEE RD, PARKTOWN, JHB/ 082560270/ howzat@iafrica.com**			
SUPERVISOR 2 (NAME & SURNAME):		% Supervision	
SUPERVISOR'S QUALIFICATIONS			
SUPERVISOR'S ADDRESS / TEL / E-MAIL:			
SUPERVISOR 3 (NAME & SURNAME):		% Supervision	
SUPERVISOR'S QUALIFICATIONS			
SUPERVISOR'S ADDRESS / TEL / E-MAIL:			

SYNOPSIS OF RESEARCH:*(Brief summary of proposed research project; between 200-300 words only; with sub-headings: an introduction and justification for study, aim/s, proposed methodology and expected outcome/s)*

[Use reverse side of this page if

more space is required]

Introduction

Skin cancers are a non-communicable malignancy that have been underreported and underexplored in South Africa and the continent at large.

Incidence of the disease is on the rise globally.

In South Africa skin cancers arise from a multifactorial risk complex involving high levels of yearly UV exposure to a sub-populace of white inhabitants of Northern European decent, high burden of HIV in the general population and poor health seeking behavior.

The incidence of skin cancers has been difficult to determine because skin cancers are not consistently logged into cancer registries. Generally, little has been published about the prevalence and epidemiology of skin cancers in South Africa and few retrospective studies exist in our setting on the subject.

Justification.

The purpose of this study is to audit and quantify the types of skin cancers presenting to the Skin Tumor clinic at Charlotte Maxeke Johannesburg Academic Hospital.

These findings will provide insight into the local burden of disease and influence Clinician awareness and resource allocation in relevant departments.

Aim

This study aims to describe the clinicopathological nature of skin cancers as well as demographic data of patients presenting with skin cancers to the clinic. The study will also add to the body of literature pertaining to cutaneous malignancies.

Methodology

The study will be a retrospective record review and quantitative descriptive study. The types and distribution of all skin cancers presenting to the clinic will be described by population group, age, gender,

anatomical site and risk factor.

The study population will include all patients seen at the skin tumor clinic at Charlotte Maxeke Johannesburg Academic Hospital between 01/01/2015 to 31/12/2019.

The study will exclude patients without histologically confirmed diagnoses.

Expected outcome

The study aims to describe the clinicopathological nature of all skin tumors presenting to the Skin Tumor clinic and add to the body of literature relating to cutaneous malignancies.

WITS ETHICS NOT REQUIRED:	Yes No	
WITS ETHICS PENDING:	Yes No	IF Y SUPPLY ETHICS
WITS ETHICS APPROVED:	Yes No	CLEARANCE CERTIFICATE AS ATTACHMENT AND INCLUDE ETHICS NUMBER HERE:
(circle appropriate symbol)*		
***Please note the final human ethics clearance certificate or animal ethics certificate must be available prior to starting research**		

As supervisor/s, I/we confirm that I have read the protocol which has been submitted for assessment.

SIGNATURE OF SUPERVISOR/S:		……
SIGNATURE PG OFFICE STAFF	REGISTERED	STAMP

……..	YES….. NO…..	

SYNOPSIS OF RESEARCH CONTINUED

PROTOCOL WITH EXPANDED LITERATURE REVIEW

1. Defining the research problem

According to data from the World Health Organisation, cancer is the leading cause of death in 60% of the world and ranks in the top 5 causes of death in a further 13% of the world.

Skin cancers are the most common malignancy in the Northern hemisphere representing 2 - 30% of malignancies in both dark and light skin types.[1] In the southern hemisphere, Sub Saharan Africa included, the incidence of skin cancers is difficult to determine as skin cancers are not consistently logged into cancer registries. Cutaneous malignancies are a growing problem in South Africa due to a multifactorial risk complex arising from the high levels of year-round Ultraviolet (UV) exposure (which particularly predisposes white inhabitants of primarily Northern European descent to skin cancers). Additionally, the high burden of HIV coupled with late health seeking behaviour leads to HIV associated skin cancers. South Africa and Johannesburg in particular boasts a diverse population of many ethnicities and is also a cosmopolitan hub that sees diverse immigrant populations. Numerous risk factors predispose the inhabitants of South Africa to several malignancies but despite the ever-present danger that is cancer, the data, studies and literature surrounding skin cancers remains inadequate.

The aim of this retrospective study is to describe the nature and quantify the extent of skin cancers presenting to the skin tumour clinic at CMJAH in Gauteng province, SA. This will add to the worldwide literature on the epidemiology of cutaneous malignancies.

2. Extended Literature overview and Motivation

Cancer is the unregulated proliferation and spread of abnormal cells within the body. Any type of cell can transform into cancerous cells and cancers can arise from any organ or tissue system in the body.

Clinico-pathological spectrum of a condition refers to the signs and symptoms manifested by a patient, and the results of laboratory studies, as they relate to the findings in the gross and histologic examination of tissue by means of biopsy or autopsy, or both.

The Clinicopathological spectrum of skin cancers can be categorised into Non melanoma skin cancers (NMSC) and Melanoma.[2] NMSC are keratinocyte carcinomas such as Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). These 2 malignancies account for most tumours in this group. Other NMSC malignancies include Kaposi's Sarcoma (KS), dermatofibrosarcoma protuberans (DSFP), cutaneous T cell lymphoma (CTCL) and Merkel cell carcinomas (MCC). Skin cancers can also be classified according to the tumour cell origin as shown in Table 6.[3]

Table 7. Tumour origin tissue and representative tumour types.[3]

Type of tumour relating to origin	Representative tumours
Keratinocytic/Epidermal (Nonmelanoma)	Basal cell carcinoma Squamous cell carcinoma Squamous cell carcinoma in situ (Bowen disease) Merkel cell carcinoma

Melanocytic	Malignant melanoma
Adnexal	Malignant tumours with eccrine and apocrine differentiation Malignant tumours with follicular differentiation Sebaceous carcinoma
Lympho-hematologic	Mycosis fungoides CD30+ T-cell lymphoproliferative disorders Skin T-cell leukaemia/lymphomas (primary or secondary) Skin B-cell lymphomas (primary or secondary) T-lymphoblastic and B-lymphoblastic leukaemia Blastic plasmacytoid dendritic cell neoplasm Skin determination in myeloid leukaemia
Neural	Malignant peripheral nerve sheath tumour
Soft tissue	Liposarcoma Fibroblastic, myofibroblastic and fibrohistiocytic malignant tumours Leiomyosarcoma Skin angiosarcoma Kaposi sarcoma
Uncertain differentiation	Pleomorphic dermal sarcoma Epithelioid sarcoma Myxo-fibrosarcoma Dermal clear cell sarcoma Ewing sarcoma

Inherited syndromes	Familial melanoma
	Gorlin syndrome (Naevoid basal cell carcinoma syndrome)
	Skin cancers on *Xeroderma pigmentosum*
	Muir-Torre syndrome

Aetiopathogenesis

The aetiopathogenesis of these skin cancers is a result of a multifactorial complex of environmental, genetic and phenotypic risk factors (Figure 5) which can be broadly categorised into extrinsic and intrinsic risk factors.

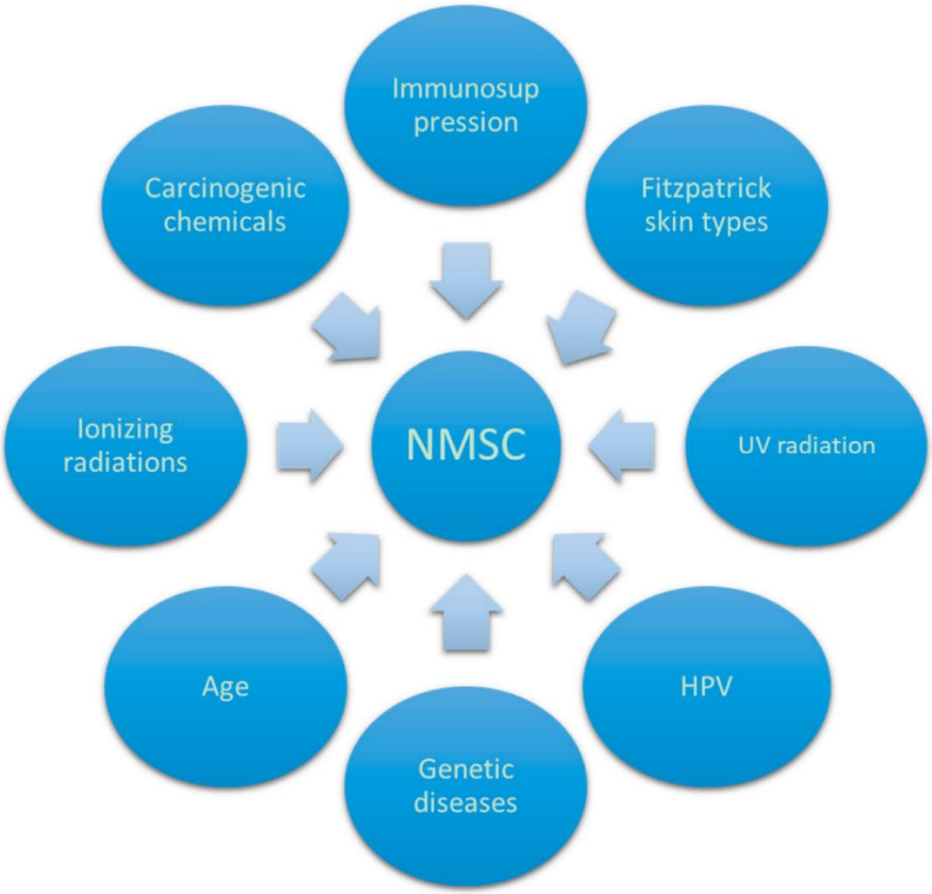

Figure 3. *Factors involved in non-melanoma skin cancer pathogenesis. UV : Ultraviolet; HPV : Human Papillomavirus.*[4]

Role of Ultraviolet radiation

Sun exposure and body site of exposure appear to play a significant role in the formation of skin cancers, particularly in BCC and SCC. This risk is greatest in residents of regions with high levels of Ultra-violet (UV) radiation.

South Africa is located at the southern tip of the continent and is found within a subtropical region spanning 22° to 34°S. The country experiences high amounts of sunshine, exceeding 2500 hours yearly in most regions[5,6].

This sunshine correlates to high levels of solar UVR (ultraviolet radiation) exposure with the mean UVI (ultraviolet index) for the country from the period 2004 to 2018 showing that during summer months the country experiences levels above 10 UVI[6]

This UVR is a major environmental risk factor for skin cancer, particularly for the Caucasian and other fairer skinned inhabitants of South Africa. Those individuals with Fitzpatrick skin types 1 and 2 are more affected. Blacks and other darker skinned ethnicities are afforded significant photoprotection due to increased melanocyte activity and larger, more dispersed melanosomes. The dose of UVR needed to produce erythema in blacks is 6-33 times higher than in whites.[1,7]

UV radiation causes direct DNA and RNA damage, resulting in covalent bond formation between adjacent pyrimidines and subsequently leading to generation of mutagenic photoproducts of radiation such as cyclopyrimidine and pyrimidine-pyrimidine adducts.[8–10]

Intermittent, recreational sun exposure, is a significant risk factor for BCC formation while chronic cumulative UV exposure is the significant risk factor in SCC formation[9]

Other artificial sources of UV have also been implicated in carcinogenesis. Indoor tanning devices that produce UV radiation are a risk factor for the development of skin cancer and as of 2015 the US Food and Drug Administration classified tanning beds as moderate risk medical devices due to this association with development of NMSCs.[11] A survey conducted in 2014 found 214 sunbed facilities operating in South Africa[12]

Phototherapy using narrow band UV-B (NB-UVB), UV-A and PUVA has also been implicated in NMSC carcinogenesis.[11,13,14]

Role of genetic conditions associated with NMSC

As already mentioned in this review, skin cancer pathogenesis occurs as a complex interplay of multiple factors. There is a subset of cases in which it occurs because of several hereditary cancer syndromes. These can be broadly categorised into : those associated with dysregulation in molecular pathways affecting cell cycle regulation and senescence; those associated with immunodeficiency and those that affect pigmentation.[15]

Familial cancer syndromes can also be broadly categorised according to the types of cancer they predominantly predispose towards[16].

Chief among familial cancers with increased risk of BCCs are Basal cell nevus syndrome (BCNS), Bazex-Dupre-Christol and Rombo syndromes. While the prevalence of these syndromes is not documented within the South African context, a retrospective analysis by Titinchi et al in 2013 found 15 documented cases at 2 Quaternary hospitals over a 40 year period[17]

Oculo-cutaneous albinism (OCA) is an autosomal recessively inherited condition and OCA type 2, also known as tyrosinase positive albinism is the most prevalent variant found in Africa.[18,19] In this variant of OCA patients have a defect in the OCA2 gene coding for the p

protein that is thought to have a role in transporting proteins to the melanosome, in stabilizing the melanosomal protein complex and in regulating melanosomal pH and/or glutathione metabolism, all of which are important to melanin production[20].This population suffers from photophobia, extreme sun sensitivity and cutaneous malignancies. Individuals with OCA have up to one thousand times a greater risk of developing skin cancers, in particular SCCs as compared to the rest of the population in their 20s to 30s.[19] According to population statistics, the prevalence of albinism in south Africa stood at 1 in 3900.[6,20]

XP is an inherited autosomal recessive disorder characterised by cutaneous and ocular hypersensitivity to UVR with subsequent irreparable DNA damage, malignant changes and possible neurologic deficit.[21] Prevalence of XP in South Africa is not documented in the national cancer registry (www.cansa.org.za accessed 19/08/2020).

In USA and Japan prevalence is 1:1000000 and 1: 100000 respectively with up to 60% of these patients developing skin cancers in adulthood, most commonly SCC.[21,22]

Other genodermatoses such as Muir-Torre syndrome and Adenosine deaminanse severe combined immunodeficiency syndrome have increased risk of other NMSCs other than BCCs and SCCs. Muir Torre is characterised by development of Sebaceous gland and visceral malignancies, while adenosine deaminase severe combined immunodeficiency syndrome is associated with high risk of dermatofibrosarcoma protuberans malignancy.

Role of immunosuppression

Immuno-suppressive states, particularly those seen in solid organ transplant recipients (OTR) and HIV positive patients have shown a well-established elevated risk of developing skin cancers.[2324,25]

Studies in HIV patients have shown an increased likelihood of developing NMSCs ranging between 2.1 to 2.76 as compared to HIV negative individuals.[24]

No increase in risk of melanoma in HIV positive patients has been definitively shown in the literature. Human Herpesvirus 8 (HHV8)has been identified in Kaposi sarcoma tissue which is the most common AIDS defining cancer seen in South Africa.[26] While the risk of AIDS defining cancers has declined since the advent of the HAART era, the incidence of non-AIDS defining cancers has increased, leading to a shift in the spectrum of HIV related cancers.[24,25] Not all skin cancers will have an increased incidence in the setting of immunosuppression and those cancers with a viral etiopathogenesis are significantly more likely to occur in the setting of immunosuppression.[27]

Pharmacological agents are routinely prescribed to OTRs and are believed to affect several immune cell types such as T lymphocytes, natural killer cells, dendritic cells and other antigen presenting cells resulting in disrupted immune surveillance and failure of the host immune system to detect and eradicate cells with precancerous changes. Cyclosporine is the most commonly used immunosuppressive medication given to OTRs to prevent transplant rejection[28], it is also used widely in a number of dermatologic and rheumatologic diseases. A study of 231 OTRs receiving cyclosporine showed that 26% of these developed cancers of which 66% were NMSC.[29] Another study conducted in Cape Town, South Africa found that 7.6% of OTRs subsequently developed cancers. SCC and BCCs were the most common cancers in whites and KS was the most common cancer in non-whites, accounting for 80% of all cases.[30]

Determination of the individual risk posed by immunosuppressant medications is very difficult and while long term exposure to immunosuppressive medications determines individual risk (Table 7), this risk is still set against all the other pathogenic risk factors mentioned in this review

Table 8. Immunosuppressant drug and skin cancer risk.[31]

Drug	Mechanism of Action	Skin cancer risk
Cyclosporine	Calcineurin inhibitor	High
Azathioprine	Anti-metabolite	High
Tacrolimus	Calcineurin inhibitor	High
Prednisolone	Glucocorticoid	Low
Mycophenolate mofetil	Antimetabolite	Uncertain

UV radiation is not only a complete carcinogen but also acts a strong immunosuppressive agent.[31,32] This was corroborated in a series of studies conducted on mice by Margaret Kripke in which UV radiation-induced tumours were transplanted into mice which were either irradiated with UV-B or not irradiated. In the irradiated population, the tumours continued to proliferate whereas the non-irradiated population rejected the tumors.[33]

Role of viruses in skin cancer pathogenesis

Over 20% of global cancer incidence is linked to infectious agents, with viral infection contributing almost 75% of the culprit infections.[34,35] The role of viruses in cutaneous malignancy pathogenesis is well documented and 3 viruses in particular are believed to play a significant role in NMSC pathogenesis. They are: Human papilloma virus (HPV), Human herpes virus 8 (HHV8) and the more recently discovered Merkel cell polyomavirus (MCV). These viruses interact with the host cell, UV radiation and host immunosuppression to bring about carcinogenesis in a process called viral oncogenesis.

Human Papilloma viruses (HPVs) are known to be associated with the formation of SCCs, while HHV8 is key in KS pathogenesis and MCV in MCC pathogenesis.[36–40]

Epidemiology of skin cancers.

Cancer ranks as the leading cause of death worldwide.[41] with an estimated 19.3 million new cases and 10 million cancer deaths having occurred in 2020.

The most frequently diagnosed cancers occurring in mankind include breast (11.7%), lung (11.4%), colorectal(10.0%), prostate(7.3%) and skin cancers (7.9%)[4142].

Cutaneous Malignancies or skin cancers are cancers arising from the uncontrolled growth of different cell types found in the skin. Skin cancers accounted for 1.52 million cancers in 2020. Of these 1.2 million were NMSC and 325 000 were melanomas. These cancers ranked 4th and 21st of the global cancers respectively in 2020.

The incidence of skin cancer globally is on the rise while mortality is stable or decreasing.[43] In the 27 year period between 1990 and 2017 the global incidence of melanoma rose by 161% while the incidence of NMSCs such as BCC and SCC rose 77% and 310% respectively.[44]

Men are approximately twice as likely as women to develop skin cancers globally.[41,45]

BCCs account for 75% of all NMSC and SCCs account for the majority of the remaining 25% of NMSCs.[16] Melanomas account for 4% of dermatologic cancers worldwide and are responsible for 60-80% of skin cancer related deaths.[46]

The incidence and mortality of skin cancers have been linked to the human development index (HDI). This index measures three key dimensions in human development : a long, healthy life measured by life expectancy; access to education measured by mean schooling

years of adult population and a decent standard of living measured by the gross national income per capita of the country.[47] HDI is inversely proportional to skin cancer mortality, higher HDI values as seen in the global west (Europe, North America and Australia) correlate to lower mortality due to better access to health awareness and healthcare in these nations. In white people skin cancers are the commonest cancer diagnosed yearly. BCCs and SCCs are the commonest and 2nd commonest of these diagnosed cancers, respectively, and their global incidence continues to increase faster than all other cancers.[48]The incidence of NMSC is double in individuals living near the equator and in Australia skin cancers account for 7 out of 8 cancers diagnosed in patients. In black people and other ethnic groups of colour Mycosis fungoides and DFSP, while being relatively rare NMSCs disproportionately affect black people and people of colour relative to people of lighter skin types.[49,50]

In North America NMSCs account of 1 out of 3 cancers diagnosed in patients yearly.[48,51] The incidence of NMSC in white populations in Europe, North America and Australia has been increasing by 3-8% per year since 1960 due to lifestyle and environmental risk factors.[43] Melanoma incidence in Europe, North America and Australia is lower than that of NMSC, however it has also been rising for several decades. Global incidence of melanoma among dark skin ethnic groups is 1 per 100 000. In whites the incidence of melanoma is 50 per 100 000. Highest incidence is found in Australia of 56 per 100 000, 14 per 100 000 in North America and 5 per 100 000 in northern Europe.[2,42,52,53] In African Americans the most common skin cancer is SCC followed by BCC.[49] BCCs occur more commonly in lighter-complexion blacks than darker complexion African americans.[7,49] Melanoma is 12 times less likely in this population group than in white Americans.[1,49] Acral-lentiginous melanoma (ALM) is the predominant variant of melanoma that occurs in darker skinned ethnic groups.[49]

Skin cancers comprise up to 4% of all malignancies in Sub-Saharan Africa (SSA).[54] SCC, KS, MM, BCC and DFSP, in decreasing order, are the most common skin cancers in SSA.[55] Most SCCs are associated with previous history of chronic ulcer (Marjolin ulcer).[55,56]

ALM is the most common presentation of MM in SSA. Up to 92% of MM cases present on acral surfaces in blacks in SSA.[55,57,58]

DFSP comprises less than 0.1% of all skin cancers. Black people have a higher incidence of this cancer than white people (0.64 per 100 000 and 0.44 per 100 000 respectively) In blacks it disproportionately accounts for up to 1,4% of NMSCs. [49,55,59]

The incidence of all cancers in South Africa is monitored by the National Cancer Registry, Eastern Cape Province registry and the South African Paediatric Tumour Registry, which catalogue. all histologically confirmed cancers. These registries do not have the resources to collect robust data on a national scale that can be used to calculate national incidences of cancers.[60] While the incidence of skin cancers is difficult to quantify in South Africa due to this lack of integrated cancer surveillance networks[60,61] the individual incidences of skin cancers are known to vary widely, affected by skin type, age and immune status.[62]

South Africa has diverse populations and skin types. Although the white population are the most susceptible to UV induced skin cancers, they occur in all racial and ethnic groups regardless of skin pigmentation.

The most commonly occurring skin cancers in South Africa are reported to be SCCs, BCCs, KS and Melanoma (CM), in that order.[63] NMSC was found to be twice as prevalent in men compared to women.

In decreasing order SCCs, BCCs and MM have the highest incidence in whites whereas in Coloureds, Asians and Blacks the order of decreasing frequency of skin cancers was BCCs, SCCs and MM.[61]

White South Africans have one of the highest incidences of MM in the world. Yearly incidence is 19-23 per 100 000 people[61,6465]

SCCs and Kaposi Sarcoma (KS) were the most frequently occurring malignancy in Blacks. In 1 study conducted in the Northern Cape Province the commonest occurring skin cancers were SCCs followed by BCCs, KS and MM[63] whereas in another study conducted in the Western Cape Province BCCS, followed by SCC, KS and MM in decreasing frequency, were the most common skin cancers in all races except blacks in whom KS followed by SCC, BCC and MM were the commonest skin cancers.[66]

In summary a review of the literature shows South Africa's burden of skin cancer is poly-etiological, impacted by Race, inherited disorders, high levels of UVR and air-borne pollutants and immunocompromise due to immunosuppressive medications and the HIV pandemic. Furthermore, there is likely under-reporting of the cancer burden in SA and shows a definite need for further studies and audits to augment the body of work involving cutaneous malignancy.

This study will aim to assess the clinicopathological spectrum of histologically confirmed skin cancers presenting to the Skin Tumour clinic at Charlotte Maxeke Hospital and detail the patients' demographics as well as associated risk factors of these cancers.

3. Study Objectives

1) To assess the clinicopathological spectrum of histologically confirmed cutaneous malignancies presenting the CMJAH Skin Tumour Clinic
2) Describe the demographics of patients being seen at the Skin Tumour Clinic

3) To outline and assess the skin cancer risk factors shown by the patients presenting to the Skin Tumour Clinic.

4. Methodology

1) Study Design

Retrospective record review. Qualitative descriptive study.

2) Study population

All patients seen at the Skin Tumour Clinic at CMJAH.

3) Inclusion Criteria

All patients seen at the Skin Tumour Clinic from 01/01/2015 to 31/12/2019 (5 Years) with histologically confirmed cutaneous malignancies.

4) Exclusion Criteria

Patients with incomplete demographic information.

Patients without histologically confirmed diagnoses.

5) Data Collection

Data will be collected from the Skin Tumour Clinic records at CMJAH utilizing a data collection form. (See appendix 1)

Data will be collected from clinical records using a data collection form and entered into an excel spreadsheet. At no point will records be removed from the site or patient identifiers entered into the study database.

6) Data analysis

As this is a descriptive study the sample size will be realized from the records available.

Baseline and demographic characteristics will be summarized using descriptive statistics (means, standard deviations for continuous variables such as age and percentages for categorical variables such as race.)

7) Ethics

Permission to access patient records will be obtained from the hospital Chief Executive Officer, Heads of Department of Dermatology and Oncology at Charlotte Maxeke Johannesburg Academic Hospital.

Ethics approval will be sought from the Human Research Ethics Committee of the University of the Witwatersrand. To protect participant's confidentiality, the data will be sent in an anonymous format, making it difficult to identify patients. The data sent will also be stored on a password protected device.

No patients will be interviewed in this study.

8) Funding

The study will be self-financed.

Item	**Estimated cost in Rands**
Printing	R800
Binding	R500
Total	R1300

9) Schedule

	Feb2021-July 2021	July2021-December 2021	Jan 2022 - May 2022	June 2022
Research protocol				
Assessment & Ethics application				
Data collection and analysis				
Write-up				

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APPENDIX TO PROTOCOL:

I. Plagiarism Declaration

II. Statement of Principles for postgraduate Supervision

III. Patient data sheet

IV. Hospital Study Research Approval

V. HREC Certificate

VI. Turnitin Plagiarism Report

DEPARTMENT OF INTERNAL MEDICINE

School of Clinical Medicine, Faculty of Health Sciences,
7 York Road, Johannesburg 2193, South Africa
Tel: +27 11 7170774 Fax: +27 11 717 2775

Plagiarism declaration for written work

I,Tapiwa Gwinji, as a postgraduate student registered for a MMed at the

University of the Witwatersrand declare the following:

- I am aware that plagiarism is the use of someone else's work without their permission and or without acknowledging the original source.
- I am aware plagiarism is wrong.
- I confirm that this written work is my own work except where I have stated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or if I have failed to acknowledge the ideas or writing of others.

Signature 

30/09/21

Date

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG | FACULTY OF HEALTH SCIENCES

STATEMENT OF PRINCIPLES FOR POSTGRADUATE SUPERVISION

IN A CONTEXT OF ACADEMIC FREEDOM AND WITHIN A FRAMEWORK OF INDIVIDUAL AUTONOMY AND THE PURSUIT OF KNOWLEDGE THIS STATEMENT IS WRITTEN IN THE BELIEF THAT THERE IS A RECIPROCAL RELATIONSHIP AND MUTUAL ACCOUNTABILITY BETWEEN SUPERVISOR AND STUDENT.

THE SUPERVISOR AND THE STUDENT:

1. Will establish agreed roles and clear processes to be maintained by both parties. In the case of join supervision everybody's role needs to be clarified.

2. Will meet regularly and as frequent as is reasonable to ensure steady progress towards the completion of the proposal, research report, or dissertation or thesis. This time varies but the normal minimum requirement for face-to-face contact spread across each year of registration is: 10 contact hours for an Honours project, 15 contact hours for a Masters by a research report and 24 contact hours for a Masters by dissertation and a PhD.

3. Will keep appointments, be punctual and respond timeously to messages.

4. Will keep one another informed of any planned vacations or absences as well as changes in his/her personal circumstances that might impact on the work schedule. Unplanned absences or delays should be discussed as soon as possible and arrangements should be made, to catch up lost time.

5. Will ensure that research on animal or human subjects is concluded according to the procedures and the requirements of the relevant University Ethics committee.

6. Will together complete progress reports on the research project, as requested by each Faculty Graduate Studies Committee.

THE SUPERVISOR

1. Undertakes to provide guidance for the student's research project in relation to the design and scope of the project, the relevant literature and information sources, research methods of data analysis.

2. Has a responsibility to be accessible to the students.

3. Will be prepared for the meeting with student. This includes being up to date on the latest work in his/her area of expertise.

4. Will expect written work as jointly agreed, and will return that work with constructive criticism within a timeframe (a suggestion of 2-4 weeks) jointly agreed at the outset of the research.

5. Will provide advice that can help the student to improve his/her writing. This may include referrals for language training and academic writing. The supervisor will provide guidance on technical aspects of writing such as referencing as well as on the discipline specific requirements. Detailed

correction of drafts and instruction in aspects of language and style are not the responsibility of the supervisor.

6. Will support the student in the production of a research report, dissertation or thesis. Provision should be allowed for adequate, mutually respectful, discussion around recommendations made.

7. Will assist with the construction of a written time schedule, which outlines the expected completion dates of successive stages of the work.

8. Will ensure the student has the opportunity to present work at postgraduate/staff seminars/national/international conferences as appropriate.

9. Will assist with the publication of research articles appropriate.

10. Will discuss the ownership of research conducted by the student in accordance with the University guidelines and rules on intellectual property, co-authorship and copyright.

11. Will ensure that the research is conducted in accordance with the University's policy on plagiarism.

12. Will ensure that the student is made aware in writing of the inadequacy of progress and/or of any work where the standard is below par. Acceptability will be according to criteria previously supplied to the student.

13. Has a duty to refuse to allow the submission of sub-standard work for examination, regardless of the circumstances. If the student chooses to submit without the consent of the supervisor, then this should be clearly recorded and the appropriate procedures followed.

THE STUDENT

1. Undertakes to work independently under the guidance of the supervisor. This includes reading widely to ensure that the literature pertinent to his/her chosen topic has been identified and consulted.

2. Is obliged to make appointments to see the supervisor and will arrange meeting times well in advance.

3. Will think carefully about how to get maximum benefit from these contact sessions by planning what s/he wants in these sessions.

4. Should submit written work for discussion with the supervisor well in advance of a scheduled meeting. The kind and frequency of written work should be agreed with the supervisor at the outset of the research.

5. Written work that is submitted should be relatively free from basic spelling mistakes, incorrect punctuation and grammatical errors. Responsibility for the accuracy of language, the overall structure and coherence of the final research report, dissertation or thesis rests with the student.

6. Undertakes to heed the advice given by the supervisor and to engage in discussion around suggestions made. Ultimately the student has to take responsibility for the quality and presentation of the work.

7. Should strive, within reasonable bounds, to maintain a focus on his/her research area and to work within the agreed time schedule.

8. Will prepare material for presentations at seminars and conferences.

9. Undertakes to submit papers for publication.

10. Agrees to honour agreements about ownership of the research and in accordance with the University's guidelines and rules in relation to co-authorship, copyright and intellectual property.

11. Will ensure that the work contains no instances of plagiarism and that all citations are properly referenced and that the list of references is accurate, complete and consistent.

12. Agrees to work in accordance with the criteria of acceptability as supplied by the supervisor.

13. Undertakes not to place the supervisor under undue pressure to submit work for examination until the supervisor is satisfied that it has reached an acceptable level of quality. We confirm that we have read and understood this statement and agree to be guided by its principles for as long as we continue to work together.

Please note: The University and Faculty endorse the **Singapore Statement** on research integrity. The principles of the Singapore Statement include honesty, accountability, professionalism and stewardship. Our responsibilities as researchers (i.e. both as students and supervisors) are as pledged in the Singapore Declaration: the assurance of appropriate "data integrity, data sharing, record keeping, authorship, publication, peer review, conflict of interest, reporting misconduct and irresponsible research, communicating with the public, complying with regulations, education, and social responsibilities (World Conference on Research Integrity, 2010)". These principles and responsibilities are important in training our postgraduate students and in promoting global research integrity. Ref: Resnik, DB and Shamoo AE (2011). The Singapore Statement on Research Integrity. Account Res. 18:71-75.

Name of student: Tapiwa Gwinji_____Student's signature: _____

Name of Supervisor: Professor Deepak Modi_____ Supervisor's signature: ____ _____

Name of Co-Supervisor: _n/a_____ Co-Supervisor's signature: n/a_____

The broad area of study is: : **Clinicopathological spectrum of cutaneous malignancies at a skin tumour clinic in Johannesburg, South Africa: A 5-year retrospective review.**

_____

Provisional submission date is: _31 August 2021_____ Degree: M. Med (dermatology) _____

Specific agreement pertaining to: ownership and joint publication, funding, may be attached and signed.

GRIEVANCE PROCEDURES: It should be acknowledged that during the course of the research that both students and supervisors can feel aggrieved. In this event, these should be dealt with as swiftly as possible by the parties involved and, if necessary, the Postgraduate Coordinators and Committees. There is, in addition, a University Grievance Policy to help guide deliberations.

Patient data sheet

Age: Gender: Male☐

Female☐

Race: Black☐ White☐ Indian/Asian☐ Coloured ☐

Not mentioned ☐

Occupation:

Risk Factors:

Fitzpatrick skin phototype: _____ Undocumented ☐

Skin signs of chronic sun damage Yes ☐ No ☐

History of sunburn during childhood Yes ☐ No ☐

FPST 1-2☐ Smoking☐ Genodermatosis ☐ : Type

_____

Immunosuppression ☐: Type _____ HIV☐ :

Duration___ Duration___

CD4__

Viral Load___

The lesion:

Duration of the lesion: _____

Macule☐ Papule ☐ Nodule ☐ Ulcer ☐ Tumour ☐

Other:

Solitary lesion ☐ Multiple lesions ☐

Localization of the lesion (please write the exact location):

- ☐ Face & Neck: _____
- ☐ Upper extremity: _____
- ☐ Trunk: _____
- ☐ Lower extremity: _____

Tumour diagnosis:

SCC☐ BCC☐ CMM☐ KS☐ CTCL☐ DFSP☐

MCC☐ Other: _____

Histologic Subtype: _____

Atypical mitosis ☐ Nerve invasion ☐ Blood vessel invasion ☐

Maturation/ differentiation ☐

Histologic staging: Epidermis☐ : S. Granulosum ☐ S. Spinosum ☐ S. Basale ☐

Papillary dermis ☐ Reticular dermis ☐

Subcutis and deeper ☐

Clinical staging: _____

Lymph node involvement ☐

Internal organ involvement ☐

Other ☐

Treatment: _____

Follow-up period:

Duration: _____

The last known status of the patient:

Cured ☐ Total remission ☐ Partial remission ☐ Relapse ☐

Exitus ☐

Lost to follow-up ☐

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (CMJAH)
OFFICE OF THE SENIOR CLINICAL MANAGER

Enquiries: *Ms. TT Mahlangu*

Email: Thandi.Mahlangu4@gauteng.gov.za

Tel: *011 488 3365*

Ref: *1/7/2*

Date: 18 May 2022

GP_202108_046

To: Dr Tapiwa Gwinji

RE: FINAL APPROVAL OF STUDY
TITLE: CLINICOPATHOLOGICAL SPECTRUM OF CUTANEOUS MALIGNANCIES AT THE SKIN TUMOUR CLINIC, CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL IN JOHANNESBURG, SOUTH AFRICA: A 5-YEAR RETROSPECTIVE REVIEW

Permission is granted for you to conduct the above-mentioned study as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not in any way incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall always be observed.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or Sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported/~~Not Supported~~

Signed by:Jayshina Punwasi
Signed at:2022-05-23 07:54:16 +02:00
Reason:Witnessing Jayshina Punwasi

Dr J. Punwasi
Senior Clinical Manager

Approved/~~Not Approved~~

Signed by:Gladys Magugudi Bogoshi
Signed at:2022-05-24 10:11:40 +02:00
Reason:Witnessing Gladys Magugudi Bo

Ms. G Bogoshi
Chief Executive Officer

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO:

Dr T Gwinji
School of Clinical Medicine
Department of Medicine
Division of Dermatology
Medical School
University

E-mail: tmgwinji@gmail.com

CC:

Supervisor: Professor D Modi
<howzat@iafrica.com>
and <HREC-Medical Research Office@wits.ac.za>

FROM:

Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2022/02/14

REF: R14/49

PROTOCOL NO: **M211121** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Clinicopathological spectrum of cutaneous malignancies at a skin tumour clinic in Johannesburg, South Africa: a 5-year retrospective review*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr T Gwinji

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M211121

NAME: (Principal Investigator)	Dr T Gwinji
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Dermatology Medical School University
PROJECT TITLE:	*Clinicopathological spectrum of cutaneous malignancies at a skin tumour clinic in Johannesburg, South Africa: a 5-year retrospective review*
DATE CONSIDERED:	2021/11/26
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Professor D Modi
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/02/14

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat 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 **November** and therefore reports and re-certification will be due in the month of **November** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator _____ Date _____

Dr. Gwinji's Article

ORIGINALITY REPORT

8%	5%	5%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

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