2 The Epidemiology of Cutaneous Melanoma in the White and Black African Population Groups in South Africa

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Abstract: In this chapter, two South African population groups, White and Black African, are compared with regard to cutaneous melanoma (CM). The incidence of CM in Black Africans is about 10% of that in Whites, explained at least in part by the protection offered by cutaneous melanin. The incidence has probably risen in Whites over the past 40 years but seems to be unchanged in Black Africans. The commonest CM subtype in Whites is superficial spreading; it occurs on various body sites, the most frequent being the trunk in males and the lower leg/hip in women. Most CMs in both male and female Black Africans are found on the lower leg and/or hip with a significant proportion being acral lentiginous melanoma, a subtype rarely seen in Whites. Risk factors including exposure to the sun,

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trauma, human immunodeficiency virus infection, albinism, age, and genetics are summarized and are likely to differ between the two population groups. The stage of CM at diagnosis tends to be more advanced in Black Africans than in Whites and, similarly, the survival rates are considerably lower in Black Africans. Reasons for the differences in CM between the two population groups are suggested.

Key words: Incidence; Mortality; Skin color; Subtypes; Sun exposure

Introduction

While surveys in several developed countries have provided accurate data on the incidence of cutaneous melanoma (CM), the resulting mortality, and the changes in these parameters over time, information from South Africa is sparse in comparison. Although reports on the epidemiology of CM in South Africa were published in the 1970s and 80s, they comprised small numbers of patients, generally attending single hospitals or clinics in one part of the country. It has remained difficult to obtain accurate figures since then, mainly due to the lack of a reliable reporting system while the country has undergone huge political, economic, and demographic changes. However, it is of considerable interest to assess what information is available as South Africa represents a subtropical country containing a multiethnic population, whose skin color ranges from deeply pigmented to fair. In this chapter, the geography of South Africa is described first, together with an explanation regarding the population groups found in this country. This section is followed by descriptions of the incidence and body sites of CM in South Africans, risk factors for CM development, the age and stage of CM at diagnosis, and mortality data. Comparisons are made throughout between the White and Black African population groups.

South Africa

GEOGRAPHY

South Africa is situated at the southern tip of Africa, spanning the midlatitudes from 22° to 34°S, and is divided into nine provinces (Figure 1). Its topography varies from coastal plains at sea level to mountain peaks reaching over 3000 m above sea level. There is a plateau at an average altitude of 1200 m, known as the Highveld, across the center of the country. High atmospheric pressure over the Highveld frequently results in relatively cloudless skies and, together with the altitude, contributes to high solar ultraviolet radiation (UVR) levels. As an illustration of the variation in the climate between the northern and southern provinces, Table 1 shows the temperature, UV Index, and the number of hours of sunshine per day in winter and summer in Cape Town (representing the South Highveld) and Pretoria (representing the North Highveld). These conditions, combined with an outdoor lifestyle, lead to the potential for excess solar UVR exposure, depending on personal phenotypic characteristics and behavior in the sun.

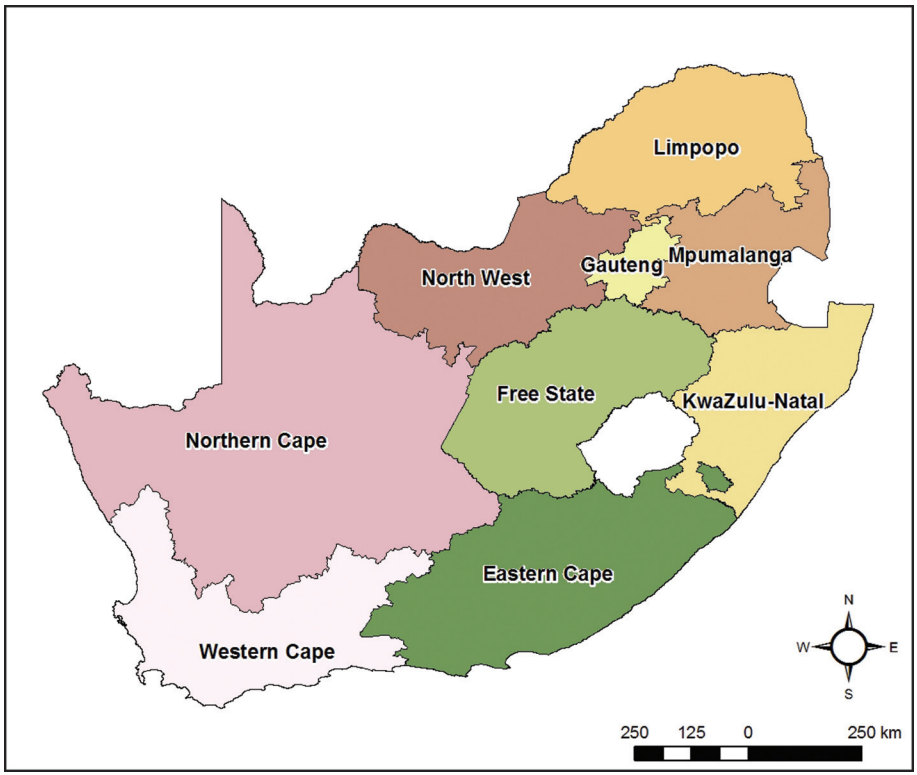

Figure 1 **The Provinces of South Africa (map drawn by M. Naidoo, Council for Scientific and Industrial Research, included with permission).**

TABLE 1 Weather Conditions in Cape Town and Pretoria (1, 2)

		Cape Town	Pretoria
	Latitude	34°S	26°S
	Altitude	0–300 m	1339 m
Average hours sunlight per day	Summer	10.2	9.1
	Winter	6.8	8.6
UV Index	Summer	9–10	11+
	Winter	2–3	4–6
Average day-time temperatures (°C)	Summer	26	30
	Winter	19	21
Average night-time temperatures (°C)	Summer	15	18
	Winter	8	5

POPULATION GROUPS

South Africa's multiethnic population comprises individuals across all six Fitzpatrick skin phototypes (3). The population is officially grouped into Black African, Colored (mixed European [White] and African ([Black] or Asian ancestry, with skin color ranging from pale to dark brown), Asian/Indian and White. The 2016 national census indicated that 80.8% were Black African, 8.6% Colored, 8.0% White, and 2.6% Indian/Asian (4). The mid-year population in 2016 was 55.9 million (4). The prevalence of several infections in South Africa is among the highest in any country in the world, particularly human immunodeficiency virus (HIV) and tuberculosis (TB). The total number of people living with HIV was estimated at approximately 7 million in 2016 (5). The incidence of TB in 2015 (including those with HIV and TB co-infections) was 834 per 100,000 people. South Africa is one of six countries that accounted for 60% of the new cases of TB in 2015 worldwide (5).

Historically, legislation restricted access for Black Africans to South African cities, but even before the repeal of the Pass Laws in 1986, the rates of rural–urban migration had increased (6). Official government projections estimate that between 2011 and 2016, the provinces of Gauteng and Western Cape experienced an inflow of 1.5 million migrants, of whom many were from the Eastern Cape and Limpopo (7). It is likely that reduced personal sun exposure, which is a recognized risk factor for some subtypes of CM, may occur with urbanization. This could be due to more time spent indoors, fewer outdoor occupations, particularly subsistence farming, and the city environment such as tall buildings and narrow streets providing more shade.

The South African National Cancer Registry (NCR) was established as a pathology-based cancer reporting system, although mandatory reporting was only legislated in 2011. Prior to this, private health laboratories withheld cancer reports from 2005 to 2007 owing to concerns regarding voluntary sharing of confidential patient data. While private health care reporting to the NCR decreased by 28% from 2005 to 2007, it is estimated that this represented a minimal impact (net decrease of <4%) on overall cancer reporting (8). The mismatch between observed and estimated number of cancers mainly impacted on affluent South Africans in all population groups who used private health laboratories since less affluent people tended to receive government-provided care.

Incidence of CM in the White and Black African Population Groups

Table 2 lists the studies that have monitored the incidence of CM in the two population groups. It is clear that the incidence is approximately 20 times higher in the White African population than in the Black African population. It is recognized that epidermal melanin provides protection against the development of skin cancer, including CM. This endogenous sun protection factor (SPF) has been estimated at up to 13.4 SPF in African Americans (17). The incidence is higher in White men than in White women, and very slightly higher in Black African women than in Black African men.

TABLE 2 **Studies in Which the Incidence of Cutaneous Melanoma (CM), Diagnosed by Histopathology, in the Black African and White Populations of South Africa has been Calculated**

Reference	Years of study	Location	Number of CM cases	Age-standardized annual incidence of CM per 100,000 persons
Isaacson (9)	1966–1975	Soweto	83	Black male, 0.72; Black female, 0.87
Saxe et al. (10)	1990–1995	Cape Town	759	White all, 24.4; White male, 27.5; White female, 22.2
Jessop et al. (11)	2001–2003	Cape Town	443	White male, 36.9; White female, 33.5
South African Melanoma Advisory Board (12)	Not stated	Cape	Not stated	All Caucasian, 69
Norval et al. (13)	2000–2004	National	3413	White male, 20.5; White female, 16.5; Black male, 1.0; Black female, 1.2
National Cancer Registry of South Africa (14)	2000	National	1506	White male, 16.7; White female, 13.1; Black male, 1.1; Black female, 1.4
National Cancer Registry of South Africa (15)	2012	National	1312	White male, 15.9; White female, 12.7; Black male, 0.8; Black female, 1.1
York et al. (16)	2008–2012	Northern Cape	135	White male, 15.8; White female, 11.8; Black male, 0.2; Black female, 0.5

The earliest study on incidence, published in 1979, was based on a small number of cases in Black Africans living in Soweto, a township close to Johannesburg with an estimated population of 1 million people (9). This was followed by two studies in Whites in Cape Town which showed an increase in incidence in both men and women when figures from 1990 to 1995 were compared with that from 2001 to 2003 (10, 11). Reported data from all of South Africa indicate that the incidence in the White population is similar to that found in European countries (18) and in Black Americans in the United States (19). Norval et al. (13) found no change in incidence in either the White or the Black African populations between 2000 and 2004, and similarly there was no increase in the national figures published by the NCR when 2000 figures (14) were compared with 2012 figures (15). It should be noted that the South African Melanoma Advisory Board in 2009 estimated the incidence of CM in Caucasians in the Cape as 69 per 100,000 (12). This figure is among the highest in the world and is

similar to current estimates in Australia (20). The basis of the Board's statement is not clear and no updates have been published since 2009.

Thus, at this point in time, there is some uncertainty about whether there might have been an upward trend in the incidence of CM in the White population in South Africa over the past 30 years, but little or no indication of an increase in Black Africans. More recent data than that of 2012 are urgently required. Second, while the risk of CM is considerably lower in Black Africans than in Whites, they make up about 80% of the population and therefore a considerable health burden is implied.

Body Sites and Subtypes of Melanoma in the White and Black African Population Groups

The percentage of CMs occurring on four body sites in the White and Black African populations in 2000–2004 in South Africa has been calculated in one study (13) and is shown in Table 3. It can be seen that there was a reasonably even distribution throughout the body in White males and females although, as also reported by Saxe et al. (10), in Whites living in Cape Town, the trunk was the predominant site in males and the lower limb and/or hip in females. The situation was markedly different in Black Africans as more than two-thirds of the CMs occurred on the lower limb and/or hip in both sexes. In confirmation, earlier surveys of Black Africans found CMs predominantly on the lower limb and sole (9), the sole and palm (21), and the foot (22). Such a distribution implies that the risk factors for CM development may differ between the White and Black African population groups in South Africa.

Superficial spreading melanoma (Figure 2) is the commonest subtype in the White population of South Africa (9, 10). Data from the NCR in 2000–2004 revealed that, when reported, the percentage of melanomas presenting as acral lentiginous melanoma (ALM) (Figure 3) was 16.6% in the Black African population compared with 0.8% in the White population (13). These figures are comparable with those reported in a US study which found that 16.7% of melanomas

TABLE 3 **The Percentage of Cutaneous Melanoma Occurring on Four Body Sites in the White and Black African Populations of South Africa, 2000–2004 (13)**

	White male	White female	Black African Male	Black African Female
Head	24.5	13.1	12.0	8.3
Trunk	37.1	22.8	12.4	6.6
Upper limb and/or shoulder	18.2	23.0	6.9	12.7
Lower limb and/or hip	20.4	41.1	68.7	72.3

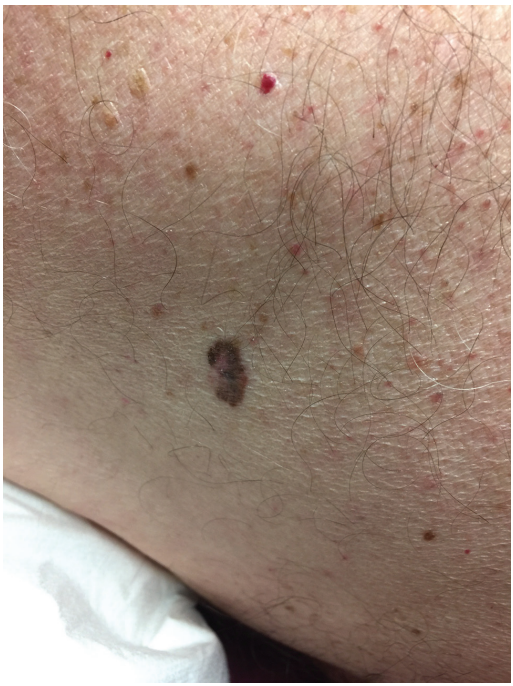

Figure 2 Superficial spreading melanoma on trunk of White male patient. Photograph supplied by Dr. W. Visser, Cape Town.

were ALM in Black Americans and only 1% of the melanomas were ALM in Whites (23). A study of 47 melanomas in Black Africans attending a referral center in Cape Town over a 14-year period (approximately 1980–1994) demonstrated that 72% were ALM, 21% were nodular, and 6% were superficial spreading (22). Hudson et al. (22) investigated plantar melanomas occurring in Black African and White patients in Cape Town between 1972 and 1985. In this period, plantar melanoma accounted for 2.1% of all the CMs in White patients, and for 73% of all CMs in Black African patients. ALM occurred in 56% of the former group but in 71% of the latter group, again demonstrating that ALM predominates in the Black African population.

Risk Factors for Melanoma in South Africa

The risk factors are complex, likely to be interrelated, and differ between population groups and anatomical site. In addition, the generation of CM is multistep, with more than one pathway being involved (reviewed in 24). One common route starts as a naevus (mole, which is a benign proliferation of melanocytes) with slow progression to melanoma *in situ*. This can then develop a vertical growth phase,

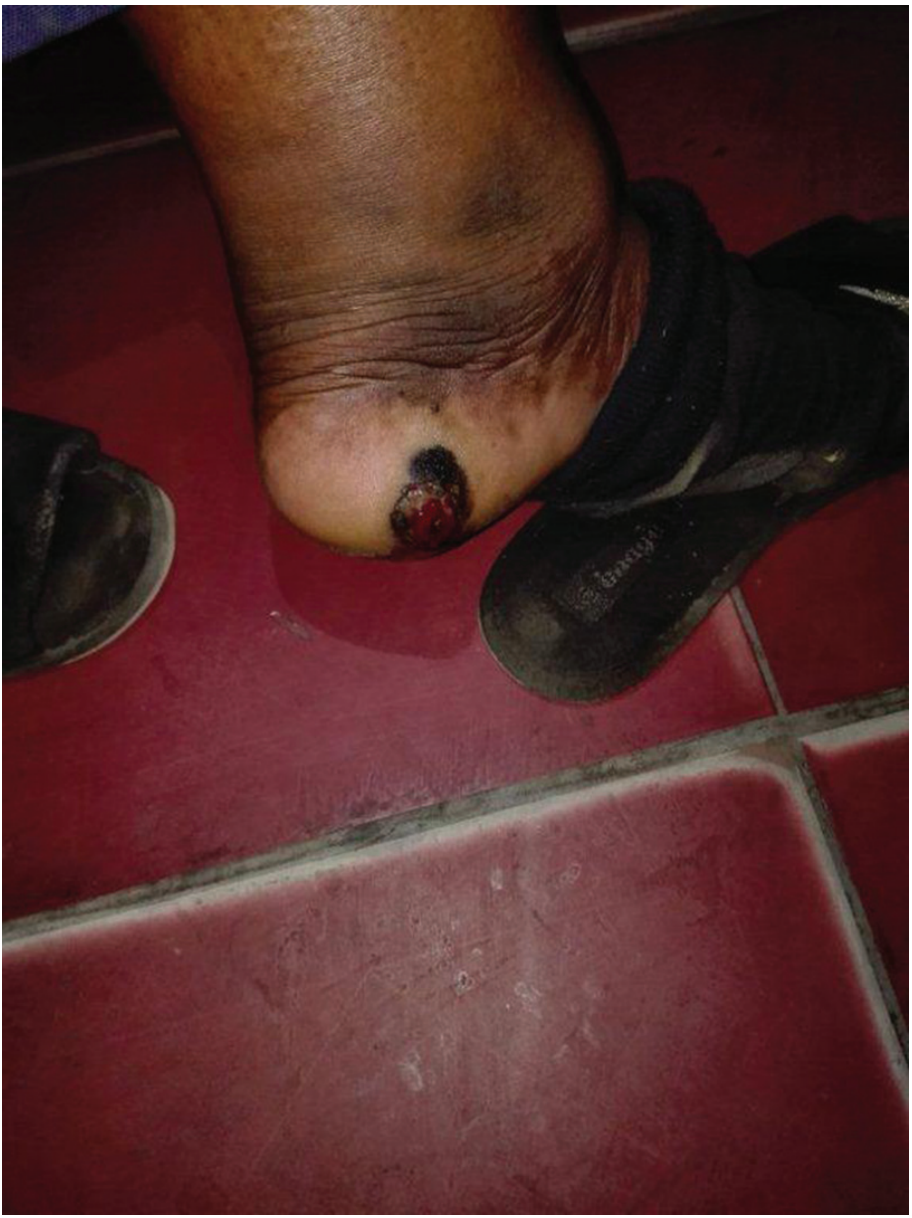

Figure 3. Acral lentiginous melanoma on the sole of a Black African female patient. Photograph supplied with permission from the patient.

invading into the dermis with the potential to metastasize. The other common route does not involve the naevi; the lesions arise spontaneously and are aggressive.

SUN EXPOSURE AND NAEVI

Solar UVR represents the major identified environmental factor with risk depending on the pattern of exposure. This differs between the subtypes of CM and has led to the hypothesis of "divergent pathways" (25). It is thought that people with few naevi tend to develop CM on body sites that are chronically exposed to the sun and show marked solar elastosis. Such sites include the face, neck, and dorsal surface of hands. Conversely, those with a high number of naevi, indicating a propensity to melanocyte proliferation, tend to develop melanomas on body sites, such as the trunk and legs. Such areas have intermittent patterns of sun exposure, including sunburn, with no solar elastosis. These pathways have been demonstrated in a large number of epidemiological and observational studies (26–28) based on Caucasians in many countries worldwide, although none have included data from South Africa. In addition, the risk of CM, as a result of sun exposure in people with hyperpigmented skin, is not clear. One analysis revealed a higher incidence of melanoma in Black Americans at lower latitudes of residence and higher mean annual UV Index in the United States, although this correlation was only significant for men (29). However, another survey of 11 cancer registries in the United States found that a higher mean UV Index was associated with an increase in melanoma incidence in Whites with some evidence for a latitude gradient in incidence. In contrast, there was no significant correlation between the UV Index and melanoma incidence in Black Americans (30). Therefore, while solar UVR is a critical risk factor in those with fair skin, it may be considerably less, or even of no importance, in those with pigmented skin.

With regard to ALM in particular, it would seem unlikely that exposure to the sun is directly involved as these tumors occur predominantly on the sole of the feet, palm of the hand, and the nail bed. However, such exposure could have systemic effects via the release of circulating immune mediators that downregulate immune responses generally (31). In addition, the pre-existing naevi on acral surfaces in deeply pigmented skin may represent a risk factor for melanoma development (32, 33). It has been reported that almost all Black people have melanocytic naevi with an average of 8.3 per person and a higher number in those with darker skin. They are predominantly acral. Approximately, one-quarter of the naevi occur on the palms and one-quarter on the soles, often near the junction between the pigmented dorsal and the nonpigmented plantar and palmer surfaces (34). As these are common sites for CM development in Black individuals, such naevi may constitute a premalignant state in those with deeply pigmented skin.

TRAUMA

As shown in Table 3, a high percentage of melanomas occur on the lower limb and/or hip in both Black African men (68.7%) and women (72.3%), and a higher incidence of ALM is found in Black Africans compared with the White population. These differences between the two population groups could be explained by

previous trauma being a risk factor in Black Africans and of less importance in Whites (32, 33). Trauma to the legs and soles could occur due to burns, scars, insect bites, and walking on bare feet.

HIV INFECTION

Currently, the estimated HIV prevalence rate in South Africa is approximately 19.2% of the total population, with a marked difference between population groups. In Black Africans, the prevalence is 15% while it is 0.3% in Whites (35). At present, almost half of those infected with HIV are being treated with antiretroviral therapy (ART) which will reduce mortality rates and may also reduce the increase in prevalence that has occurred in recent years. As persistent infection with HIV leads to a reduction in circulating CD4+ T-lymphocytes, immunodeficiency, opportunistic infections, and eventually AIDS, there is the potential for an increased risk of melanoma development in HIV-infected individuals. In addition, about 11% of HIV-infected individuals receiving ART in sub-Sahara Africa are older than 50 years, a time of increased susceptibility to a range of tumors (36). There is a wide range of HIV-associated malignancies, mostly linked with infectious agents such as Kaposi sarcoma with human herpes virus-8, Burkitt lymphoma with Epstein–Barr virus, and squamous cell carcinoma of the skin with human papillomavirus. Therefore, there is interest in determining whether HIV infection increases the risk of CM. A meta-analysis of studies performed in six countries in 2007 involving half a million patients, probably all Caucasian, indicated that the standardized incidence rate for melanoma was 1.24 per 100,000 in HIV/AIDS patients compared with uninfected controls (37). Another meta-analysis, 7 years later, compared the risk of melanoma in patients with HIV/AIDS living in North America and Europe before ART became available and after 1995 when ART was in common use (38). In about half of the included studies, an adjustment was made for ethnicity on the basis of skin color (White, Black, and other). It was found that the pooled relative risk for the association between HIV/AIDS pre-ART was 1.28 and post-ART was 1.50, when adjusted for ethnicity, compared with uninfected control groups. Thus, there is evidence that HIV infection does increase the risk of melanoma. As far as we are aware, no studies have been undertaken to monitor the relative risk of melanoma in White and Black African people with HIV/AIDS in South Africa.

SEX

A balance between the genders in Caucasians in the incidence of CM has been recorded in countries with high UV Indices, but a predominance of females over males in places with lower UV Indices (39). As seen in Table 2, the incidence of CM is higher in men than in women in the White population group in South Africa and is only slightly higher in women than in men in the Black African population group. It is possible that there are more White men than women in South Africa who have outdoor occupations, who might wear fewer clothes than women, and who use less personal photoprotection than women. Whether any gender difference in incidence or body site distribution goes beyond societal differences is uncertain at present (40, 41).

AGE

The incidence of most common cancers increases with age in both males and females worldwide. This is thought to be due to the many genetic changes involved in carcinogenesis, in addition to age-related reductions in the efficacy of the immune system. With regard to South Africa, among 595 Whites diagnosed with primary CM, the median age at diagnosis was 51 years in women and 56 years in men (10). Age-specific rates increased with age among the study sample with the steepest trends in the age group of 55 years and above. Another study reported that the mean age at presentation of melanoma among Black Africans in Cape Town was 60.5 (22), while data from the NCR indicated that the mean age in both Black African and White South Africans was approximately 55 (13). No significant difference between Black Africans and Whites in the percentage of the cases presenting under the age of 40 was demonstrated, indicating that age as a risk factor did not differ with skin color (13). In those patients living in Cape Town who developed CM on the sole of the foot or nail bed, the mean age was 56 (range 19–83) in Whites and 60.9 (range 30–83) in Black Africans (42). Therefore, there is no significant age difference between these two population groups with regard to this subtype of melanoma.

ALBINISM

Oculocutaneous albinism (OCA) is a group of congenitally inherited developmental disorders which affect the generation of pigment in the skin, iris, and hair. In South Africa, the commonest type in the Black African population is OCA2 in which the skin color is creamy white with yellow and/or light brown hair. The estimated prevalence of OCA2 in South Africa is 1 per 3900 but is considerably higher than this in some tribes (43). While people with OCA have a greatly increased susceptibility to nonmelanoma skin cancers (NMSC: squamous and basal cell carcinomas), most developing by age 20–30 years, they rarely present with CM. For example, no melanomas were found in 111 OCA patients in Johannesburg, of whom 25% had NMSC (44) and only one had an ALM in 86 OCA patients in Northern Tanzania (45). Most recently, it was reported that none of the 16 patients with OCA in Bloemfontein had a current or previous diagnosis of CM, although the majority had dendritic freckles on sun-exposed skin and were diagnosed with NMSC (46). The reason for very low frequency of melanoma in OCA may include under-reporting, especially as at least half are amelanotic (47). In addition, the life expectancy in those with OCA may not be long enough for the CM to become apparent, or the OCA2 skin color, although pale, may still offer some protection against the mutagenic effects of solar UVR in melanomagenesis.

GENETICS

Genetic susceptibility to CM is recognized and indeed a study in Sweden calculated that the familial risk for offspring of affected parents is about 2.6 times or higher if a parent has been diagnosed with CM when aged younger than 50 (48). Overall, it is estimated that 21% of the susceptibility to CM is due

to genetic factors (49). A complex range of genes is involved such as CDKN2A (a regulator of cell division) and MDm2 (a negative regulator of the p53 tumor suppressor protein). Other genes may confer a lowered risk of CM development (50). We have not found any studies comparing the genetic makeup of the White and Black African populations in South Africa, and so the contribution of inherited gene mutations in these groups as risk factors for CM is unknown at present.

Stage of Melanoma at Diagnosis in the White and Black African Population Groups

The stage of disease at diagnosis tends to be lower in Whites compared with Black Africans. Among 44 White South Africans, for example, 40 presented with Stage I melanoma of the foot, two with Stage II, one with Stage III, and one with Stage IV disease (51). An almost equal number of Black Africans were diagnosed with melanoma at Stage I (n = 30) compared with Stages II, III, and IV combined (n = 34) (22). A similar but much larger survey in the United States indicated that 16.7% of Black Americans and only 3.9% of Whites presented at Stage IV (23). Lodder et al. (52) reported that, out of 170 Black South Africans with ALM in Pretoria, 55 were Stage I, 90 were Stage II, and 25 were Stage III at the time of presentation, indicating the relatively advanced stage of disease at initial diagnosis. This point is further emphasized by 58% of the tumors being greater than 40 mm in at least one dimension on initial examination (52).

Recent evidence suggests that CM is being detected earlier, as indicated by low-stage depth increasing by 72% annually among patients in private and public health care systems in the Northern Cape Province (16). This remains to be validated in other provinces, especially given the known difficulties in early diagnosis in darkly pigmented skin types that typically lead to late presentation and the likelihood of more advanced presentation (53). Moreover, access to treatment is very poor in the public sector. This could also be related to a lack of clinical dermatology training among general practitioners. An inability to pay for appropriate treatment also contributes to more advanced stages of disease at presentation. In addition, the melanoma subtypes occurring in Black Africans may be more aggressive than in Whites, and there are likely to be significant differences in socioeconomic status and lifestyle behaviors between the two population groups.

Mortality Data for Melanoma in the White and Black African Population Groups

To date, there is little precise information on the causes of mortality in South Africa, although GLOBOCAN, which provides estimates of cancer incidence, mortality, and prevalence worldwide, reported 513 deaths due to CM in 2012 (54). One early study found that the 5-year survival rate in Black Africans with CM was 20% compared with 42% in the White population group (21). In Pretoria, 44 Black African patients out of 63 with CM died within a mean of 1 year of

presentation, while 16 were alive after a follow-up of 5 years (22). A 15-year study in Pretoria included 175 Black African patients, most of whom presented with ALM at an advanced stage (52). There were 128 documented deaths, of which 35 patients died from melanoma within 1 year of presentation. At 3 years, 92% were dead or had residual disease.

Late presentation and the malignant nature of ALM, with its propensity to metastasize, are likely to lead to poorer prognosis in Black Africans compared with White patients. Furthermore, the lack of self-examination and screening for cultural and financial reasons, plus the shortage of clinical facilities for many Black African people, particularly in rural areas, may be contributing factors.

Conclusion

The risk of developing CM is considerably less in the Black African population than in the White population in South Africa. Also, the common subtype of melanoma is superficial spreading in Whites, while ALM predominates in the Black Africans. A range of factors that may increase the risk of CM includes exposure of the skin to the sun, the presence of naevi, body sites of trauma, HIV infection, sex, age, and the occurrence of albinism and genetics. These are likely to differ markedly between the two population groups. The stage of CM at diagnosis tends to be more advanced in the Black Africans than in the Whites, with an associated reduced survival rate. Reliable published data on all these aspects are sparse and almost entirely lacking in recent years. In particular, it is important to ascertain if the incidence of CM in the White population is increasing, and whether improved public awareness about the dangers of CM is leading to earlier detection in all population groups. Finally, as Black Africans represent around 80% of the South African population currently, even the low incidence in this group implies considerable social and financial costs.

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