

## Review Article

# Cutaneous Malignant Melanoma in Skin of Color Individuals

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## Abstract

Cutaneous malignant melanoma (CMM) is a malignancy with a worldwide incidence. Literature is replete in the Caucasian population, but in skin of color, there is a dearth of literature. Documented reports of the epidemiology of cutaneous melanoma reveal a low incidence in the skin of colour individuals (SCIs). However, this incidence is rising. It is also documented that when CMM does occur, it is commonly acral, unlike in Caucasians in whom it is truncal, and the most common histopathological pattern is acral lentiginous melanoma. There are as yet no observed differences in the histopathology of melanoma in individuals with skin of color and that in Caucasians. SCIs have a low awareness of CMM with consequently advanced lesion presentation, ulcerated lesions, and poor survival compared to Caucasians. The genetics of CMM in the skin of color has not been well studied. The only available study of the genetics of melanoma reveals a difference in melanoma genetics between SCIs and Caucasians. In SCIs, due to the low incidence of cutaneous melanoma, cutaneous melanoma is commonly misdiagnosed. This misdiagnosis can be both clinical and histopathological. Awareness of the features of cutaneous melanoma and sun protection practices is poor in individuals with skin of color. A high index of suspicion should be entertained of any hyperpigmented lesion in any SCI, especially if it is acral and a histopathological assessment should be made as early treatment improves survival.

**Keywords:** Caucasians, differences, malignant, melanoma, skin of color

## INTRODUCTION

Cutaneous malignant melanoma (CMM) is uncommon in the skin of color individuals (SCIs), making documented studies in this population few and mostly outdated. In a study of incidence rate covering 67.2% of the US population between 1996 and 2006 in people aged 15–39 from 38 cancer registers, a rate of < 1% was recorded in SCIs.<sup>[1]</sup> Most of the studies on the pathogenesis, clinical features, histology, and interventions in CMM have been in Caucasians.<sup>[2]</sup>

The low incidence rate of CMM in SCI has been attributed to the constitutive pigmentation of the skin.<sup>[3]</sup> Following a study of 3500 women from different geographic areas, DNA damage of melanocytes was found to be dependent on skin color with decreased DNA damage in dark skin.<sup>[3]</sup> The low incidence of CMM in SCI makes reviews and comparison of studies difficult as most sample sizes are small and studies are few. Melanoma-specific survival (MSS) rates differ between ethnic groups, with SCI having lower 5-year survival rates than Caucasians even after treatment.<sup>[2]</sup>

Delayed and advanced presentation in SCI with melanoma and its consequent poor prognosis is attributed to a low

perception of risk of melanoma, low awareness of its risk factors and its clinical presentation.<sup>[4-7]</sup> Available literature from different countries of the world shows various prevalence rates of malignant melanoma. Also, other features including the age of onset, area of onset, anatomic sites affected, clinical classification, histopathology, the severity of the disease, disease progression and associated diseases are all well documented, especially in Caucasians.

Differences in clinical presentation, disease progression, and management options in different ethnic groups have also been documented; however, this is not the case in SCIs. There is little documented knowledge of genetics, clinical and histological differences between melanoma in SCI and other skin types. Increased knowledge of the difference in clinical and histological characteristics between melanoma on the skin

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of SCI and other skin types would improve patient management by being able to provide accurate information to patients and their families and thus contribute to better survival.

The aim of this review is to document the clinical, genetic, histopathological characteristics, and variants of melanoma in SCI. Also, to highlight differences between melanoma in SCI and Caucasians.

## MATERIALS AND METHODS

Four electronic databases (PubMed, Google Scholar, Ovid, and Embase) were systematically searched to find articles published on CMM using the following search words; cutaneous melanoma, blacks, whites, Caucasians, skin of colour, ethnic skin, African Americans, nonwhites, differences and comparison between ethnic groups. In addition, the reference lists of selected articles were checked for additional relevant articles.

SCIs in this study refers to all groups with dark skin of African descent (African Americans, Africans, Africans with mixed ancestry).<sup>[8]</sup> One hundred and seventy-three papers were reviewed, with sixty-six specifically addressing cutaneous melanoma in people of SCI. Papers of studies specifically conducted in SCI and papers specifically addressing differences in SCI and Caucasians were reviewed. Fifty-eight papers dated from the year 2000 to date were finally chosen for review. Older manuscripts were excluded as they either did not contain information different from those in the selected papers or did not address the study aims. Data were entered into SPSS version 18. Simple frequencies are presented.

## EPIDEMIOLOGY OF CUTANEOUS MELANOMA

Epidemiological studies have documented the occurrence of CMM in SCI, although the incidence is low compared to that of Caucasians and other ethnic groups.<sup>[2]</sup> The incidence rate of CMM varies between 21.6 and 50 per 100,000 persons per year in Caucasians and 1.0–1.2 per 100,000 persons per year in SCI.<sup>[9]</sup> Age-adjusted incidence rates per 100,000 persons per year in men and women vary between ethnic groups.<sup>[10]</sup> This varies between 9.55 and 17.2 in Caucasian males, 7.88 and 11.3 in Caucasian females to 0.69 and 1.2 in SCI males and 0.7 in SCI females.<sup>[10]</sup> A 1.5 fold increase in the incidence of CMM in Caucasians from 18.2 in 1992 to 26.3 in 2004 was noted, and for the same period, a 1.6 fold increase in incidence in SCI from 0.5 to 0.8.<sup>[10]</sup> Incidence data of CMM extracted from Surveillance, Epidemiology and End Results (SEER) covering different time periods revealed that SCI accounted for 0.4%–1.0% of CMM while Caucasians accounted for 95%–99%.<sup>[2,5,11]</sup>

Epidemiological studies of cancers in Africa revealed that melanoma made up 31% of cancers in Cotonou,<sup>[12]</sup> 9.9% in Nigeria.<sup>[13]</sup> In Togo, no single case of melanoma was diagnosed from 1984 to 2008.<sup>[14]</sup> Evaluation of time trends in melanoma incidence in SCI shows conflicting results.

Some reports show no change in incidence,<sup>[4,5]</sup> while another report showed a 1.6 fold increase in melanoma from 0.5 to 0.8/100,000 persons/year.<sup>[10]</sup> The reason for this difference in reports may be due to the fact that these data were extracted from different geographical locations in the US though it was done in the same period.

The average age at diagnosis of melanoma in SCI varies between 56 and 60 years, although, most people are diagnosed between age 50 and 64 years.<sup>[5,11]</sup> Acral lentiginous melanoma (ALM), the most prevalent type of CMM in SCI is diagnosed mainly a decade later in the age range of 60–70 years.<sup>[15]</sup> Data from SEER show that SCI is diagnosed at a slightly older age than Caucasians, with an average of 59 and 55 years, respectively.<sup>[16]</sup>

Differences exist in the characteristics of CMM between males and females of SCI. More males than females are diagnosed with CMM. Most studies show male-to-female (M: F) ratios of between 1–1.7:0.6–1.3.<sup>[2,13,17]</sup> Though Ultraviolet B radiation (UVB) is not thought to be a major risk factor for melanoma in SCI, it was found following a study of the association of UVB with melanoma in SCI that, in males, there was an increased risk of death for a 50% increase in UVB radiation. No such increase was observed in females.<sup>[11]</sup>

## RISK FACTORS FOR MELANOMA IN SKIN OF COLOUR INDIVIDUALS

Melanoma development in an individual is dependent on the individual's phenotype, genotype, and environmental factors.<sup>[18]</sup> The risk factors of CMM in SCI is not as well known as that in Caucasians in whom extensive studies have been done, and the risk factors are well known.<sup>[18,19]</sup> Ultraviolet radiation is not thought to be a major risk factor for melanoma in SCI. A study comparing ultraviolet (UV)-induced DNA damage in people of different ethnicity showed that all skin types experience DNA damage following UV exposure.<sup>[20]</sup> This study also showed that the SCI skin recovers over hours with little or no residual DNA damage one week after ultraviolet radiation (UVR) exposure.<sup>[20]</sup> This is unlike what happens with Caucasian skin, which takes days to recover and has residual DNA damage one week after UVR exposure.<sup>[20]</sup>

The skin of SCI has a high melanin content, and this is protective against the development of melanoma in this group of people. Following a study of 3500 women of African descent DNA damage was higher the lighter, the skin phenotype.<sup>[3]</sup> SCIs may require high environmental exposure to sunlight to induce CMM.

Trauma as a risk factor for melanoma has also been evaluated and was not found to be an aetiological factor in SCI.<sup>[21,22]</sup> It is thought that, if the trauma had been an aetiological factor for melanoma, the rate of subungual melanoma would have been higher than it is now as the hand is commonly subject to trauma. Other reported risk factors for melanoma in SCI include albinism, radiation therapy, immunosuppression, burn

scars, pre-existing nevus (especially acral), and congenital naevus.<sup>[22,23]</sup>

In summary, the risk factors for melanoma in SCI are still uncertain with conflicting reports from various studies. This review raises the hypothesis that melanoma in SCI may have a different histogenesis from melanoma in Caucasians.

## CLINICAL FEATURES

Cutaneous melanoma in SCI presents as a dark macule or patch with a gradual increase in size commonly on the plantar and palmar aspects of limbs, unlike what is observed in Caucasians in whom melanoma is commonly truncal [Figure 1].<sup>[19,24,25]</sup> Subungual melanomas present as a pigmented band wider than 3 mm on the nail with Hutchinson's sign. They exhibit pigment variation, rapid growth in size, and these lesions are usually solitary<sup>[19]</sup> [Figure 2].

The anatomical distribution of melanoma differs between SCI and Caucasians. SCIs tend to have melanomas in nonsun exposed areas, unlike Caucasians who have melanomas in sun-exposed areas. In SCI, 79%–93.7% of lesions are acral.<sup>[13]</sup> A comparison of the percentage anatomical distribution of melanomas between SCI and Caucasians is shown in Table 1.<sup>[2,5]</sup> Differences also exist in the site of melanoma presentation between genders both within and inter-ethnic groups [Table 1]. Caucasian men seem to have most of their melanomas on the trunk while Caucasian women have most of their melanomas on their lower limbs. Amongst SCI, melanomas are mainly on the lower legs, but women appear to rarely have melanomas anywhere else unlike the men who have melanomas in other body sites. It is not known why this difference in the determiner distribution of melanomas occurs.

## MISDIAGNOSIS

Melanomas in SCI are commonly misdiagnosed as other pigmented skin lesions mainly because of the pigmentation. Melanomas may be misdiagnosed as fungal infections, subungual hematoma, tinea nigra, pigmented basal cell

carcinoma, tinea corporis, tinea manuum, talon noir, erythema dyschromicum perstans, fixed drug eruption, melasma, localized argyria, exogenous ochronosis, melanotic lupus erythematosus, Berloque dermatitis, and pigmented viral warts.<sup>[19,26,27]</sup>

## DELAY IN PRESENTATION

SCIs tend to present late, with delays of up to 5.6 years before diagnosis.<sup>[15]</sup> Most of these patients present because of bleeding and enlargement of a pigmented skin lesion.<sup>[15]</sup> Postulated reasons for the delay in presentation include a misconception of never getting melanoma, poor accessibility of health care, lesions in unusual sites (plantar, subungual). Specifically, people with plantar melanoma present late with a mean duration of 3.1 years.<sup>[12]</sup>

MSS is lower in SCI than in Caucasians. The 5-year survival for thin melanomas is lower in SCI than in Caucasians, but they have almost the same survival in advanced melanomas.<sup>[2]</sup> Zell *et al.* documented a 5- and 10-year survival of 79.8% and 64.4% respectively in Caucasians compared to 63.2% and 44.9% in SCI.<sup>[28]</sup>

## SURVIVAL

In a study of ALM, the 5- and 10-year MSS in SCI was 77.2% and 69.4%, respectively compared to 82.6% and 71.5% in Caucasians.<sup>[29]</sup> ALM results in a higher mortality in SCI mainly because of thicker tumors and late-stage presentation. However, when Breslow thickness (BT) is > 2.0 mm, there is no observed difference in survival between Caucasians and SCI.<sup>[29]</sup> Survival with ALM is poorer than in other cutaneous melanomas (CMM); CMM is associated with 5 and 10-year survival of 91.3% and 87.3% compared to 80.3% and 67.5%, respectively, in ALM.<sup>[29]</sup>

Furthermore, survival following surgery is low in SCI.<sup>[16]</sup> The 10 years MSS was 73% compared to 88% in Caucasians irrespective of the type of surgery.<sup>[16]</sup> This low survival is due to SCI presenting more with advanced melanomas.



Figure 1: Acral melanoma on the sole



Figure 2: Subungual melanoma involving the second left toe

**Table 1: Distribution frequency of melanomas between genders in skin of colour individuals and caucasians**

Site	Skin of colour individuals (%)		Caucasians (%)	
	Males	Females	Males	Females
Head and neck	12	2	22	13
Trunk	14	7	40	23
Upper limbs	14	2	21	25
Lower limbs	50	63	9	32
Unknown	10	26	9	6

Survival in SCI is also stage dependent. Stage 1 disease had 52.68% and 11.07%, 5- and 10-year survival, respectively.<sup>[30]</sup> When compared to Caucasians; survival from Stage 1 CMM is 75.97% in Caucasians and 52.68% in SCI and survival from local disease occur in 58.8% of Caucasians and 43% of SCI.<sup>[16,30]</sup> Survival is also dependent on the site of melanoma, with acral melanoma being associated with a low survival rate compared to truncal melanoma.<sup>[30]</sup>

## TREATMENT

Caucasians and SCI are offered the same modalities of treatment (surgery, radiotherapy, immunotherapy, chemotherapy). However, amputation occurs more commonly in SCI.<sup>[28]</sup> Amputation is carried out in 10.5% of SCI compared to 0.3% of Caucasians mainly because of the presentation of ALM in people of African descent.<sup>[28]</sup> Due to late-stage presentation, only 71.7% of SCI have surgery compared to 83.4% of Caucasians<sup>[16]</sup> [Table 2].

## PROGNOSIS

Melanomas in SCI carry a poor prognosis in contrast to what is observed in Caucasians, although for the advanced stage at diagnosis, there is no difference in prognosis<sup>[16,31]</sup> [Table 2]. Factors responsible for poor prognosis are; advanced stage lesions, delayed presentation, ulceration of lesions, site of melanoma, and type of melanoma.<sup>[31-33]</sup> Subungual melanoma, acral lesions, increased BT, and histological subtype of ALM convey a poor prognosis.<sup>[29,31,34]</sup> These melanomas present with increased tumor thickness, which is one of the prognostic signs for melanoma.<sup>[29,31,32]</sup>

## MELANOMA STAGING

When it comes to staging of melanoma, SCI from various studies are more likely to present with 19%–55% Stage 3 and Stage 4 melanoma with only 11%–37% presenting with Stage 1 and Stage 2 melanomas.<sup>[4,5]</sup> This advanced stage presentation in SCI has been attributed to many factors, including the site of melanoma lesions, the atypical features of melanoma in SCI, and the perceived low risk of melanoma.<sup>[6,25]</sup> Conclusions drawn from data on ALM from 17 Cancer Registries covering 26% of the US population is that ALM, the main presentation in SCI is associated with an advanced stage at presentation, with increased tumor thickness and confers a poor prognosis.<sup>[29]</sup>

**Table 2: Comparison of cutaneous melanoma between skin of colour individuals and Caucasians**

Site	Skin of colour individuals (%)	Caucasians (%)
	Lower limbs and hips	39–81
Trunk	6–19.7	31–34
Head and neck	5.1–11.9	19.4
Upper limbs and shoulders	10.7–12.9	24
Treatment		
Rate of amputations	10.5	0.3
Rate of surgery	71.7	83.4
Disease stage presentation		
Local disease	65.1–69	80
Regional and distant metastasis	24.5–52	10.1–16
Early stage presentation incidence/100,000	23.6	0.7
Late stage presentation incidence/100,000	1.2	0.5
Sun protection behaviour		
Sun screen	15.4	30.1
Wide brim hat	29.3	20.7
Sun glasses	47.1	62.9

## COST

The cost of treating melanoma is high.<sup>[35]</sup> The average cost of year per potential life lost in an SCI due to melanoma is \$413,913 in the United States of America (USA).<sup>[36]</sup> Patients on Medicaid tend to present later than people who can afford private insurance, and a low socioeconomic status leads to presentation with advanced lesions.<sup>[35]</sup>

## AWARENESS AND PERCEPTION OF RISK OF MELANOMA

The level of perception of the risk of melanoma in SCI is low.<sup>[6,37]</sup> SCIs view their risk of melanoma to be low and they also have a low awareness of the typical features of melanoma.<sup>[7,38,39]</sup> Pain is thought to be the sign of melanoma and they also have inaccurate beliefs about melanoma and do not think that it is associated with their lifestyle.<sup>[38]</sup>

There is a misconception of cutaneous melanoma in SCI both by patients and doctors.<sup>[40]</sup> Only 17% of SCI compared to 61% of Caucasians see the doctor for a complete skin examination.<sup>[7]</sup> Total body skin examination in SCI both by patients and dermatologists is low due to a low perception of risk of melanoma in SCI.<sup>[7]</sup> No advice on sun protection is given to SCI group of patients. Educating SCI about the clinical features of melanoma and risk of melanoma will lead to early diagnosis and improved survival in this group of people.

## PREVENTION PRACTICES

Sun protection practice is low in SCI. SCIs were found to be less likely to use sunscreen compared to Caucasians in a study of sunscreen use.<sup>[41]</sup> A study of sun protection practices

amongst postal workers revealed the following practices; only 15.4% of SCI compared to 30.1% whites use sunscreen, 29.3% of SCI compared to 20.7% of Caucasians use wide brim hats, and only 47% SCI compared to 62.9% of Caucasians use sunglasses.<sup>[41]</sup> In another study of 50 dermatologists, sun protection counseling was not routinely given to SCI despite the thinking that sun protection is important in SCI.<sup>[42]</sup>

Educating SCI about the clinical features of melanoma and their risk of melanoma will lead to protective behavior, prevention, and early diagnosis of melanomas.<sup>[32,39]</sup> Careful examination of the acral site should be advised in SCI as most of the melanomas in this group is acral.<sup>[33]</sup> Public health education on the risk of melanoma, screening for recurrences should be advocated in SCI. Regular skin self-examinations and doctor examinations should be performed in SCI with advice on sun protection habits.<sup>[19]</sup>

## HISTOGENESIS OF MELANOMA

Currently, there are no documented differences in the histopathology of cutaneous melanoma between SCI and other ethnic groups. The same histological features are observed. However, the differing subtypes, aetiological factors, and anatomic site of occurrence have raised questions about differences in melanoma genesis between these two populations.

## HISTOLOGICAL CHARACTERISTICS

Studies on the histological type of melanomas in SCI reveal ALM to be the most predominant subtype.<sup>[2,5,16]</sup> This is in contrast to what is seen in Caucasians who predominantly present with superficial spreading melanoma (SSM).<sup>[5,16]</sup> The prevalence of the histological subtypes of melanoma in African skin is shown<sup>[2,5,16,28,34]</sup> in Table 3.

ALM is the most prevalent melanoma in SCI, followed by SSM, nodular melanoma (NM), and lentigo maligna melanoma (LMM). The least frequent subtypes of melanoma in SCI are desmoplastic and amelanotic melanoma.<sup>[2,5,24,34]</sup>

Also the proportions of the different subtypes of melanoma have been observed to differ by gender in SCI<sup>[43]</sup> [Table 4]. Thus in SCI, men present more with ALM while females present more with SSM. The reason for this difference is not known. On the other hand, in Caucasians, there is no difference between men and women in the subtypes of melanoma as the most prevalent subtype in both genders is SSM.

## BRESLOW THICKNESS

The reported BT is more in SCI, being 1.2–1.3 mm compared to 0.66–0.8 mm in Caucasians.<sup>[41]</sup> Thirty-two to fifty percent of SCI present with a BT of > 3 mm and only 12% with a BT of < 1–0 mm.<sup>[44]</sup> A BT of > 6.5 mm has been recorded in SCI.<sup>[38]</sup> BT in ALM is thicker than in other histological subtypes of melanoma.<sup>[24]</sup>

**Table 3: Comparison of melanoma subtypes between skin of colour individuals and Caucasians**

Subtype of melanoma	Skin of colour individuals (%)	Caucasians (%)
Acral lentiginous melanoma	10.4–66	0.4–2
Superficial spreading melanoma	4–23	18–26.5
Nodular melanoma	0.8–22.5	6.8–5
Lentigo maligna melanoma	2.4–8.9	3.7–13.8
Amelanotic melanoma	0.0–0.8	0.4–0.5
Desmoplastic melanoma	0.85–1.4	0.4–2.2

**Table 4: Comparison of subtypes of melanoma between males and females skin of colour individuals**

Subtype of melanoma	Males (%)	Females (%)
Acral lentiginous melanoma	12.1–19	13.7–16
Nodular melanoma	4.7–10	6–9
Superficial spreading melanoma	7–16.1	22
Lentigo maligna melanoma	2–4.7	0–5.1

## ULCERATION

Ulcerated lesions are frequently seen in 10.4%–59% of SCI.<sup>[5,16,28]</sup> This is in contrast to Caucasians in whom only 4.4%–5.0% present with ulcerated lesions.<sup>[5,16,28]</sup> Ulcerated lesions confer a poor prognosis as patients with ulcerated lesions have < 31 months survival compared to 86 months people with no ulceration.<sup>[6]</sup> As previously stated, SCI with ulcerated lesions tend to present more with advanced disease; 48% present with Stage 3 and Stage 4 disease, while only 11% present with Stage 1 and Stage 2 disease.<sup>[6]</sup>

## CLASSIFICATION OF MELANOMAS

There are four main classifications of melanoma based on the anatomical site of origin and intraepidermal growth pattern. The four subtypes are; ALM, SSM, LMM, and NM. In SCIs, the most common subtype of melanoma is ALM followed by SSM, the NM and least of all LMM.<sup>[2,5,16,24,28,34]</sup>

ALM is the most prevalent subtype of melanoma in SCI and it occurs mostly on the sole of the foot, one of the least sun-exposed areas of the body.<sup>[2,24]</sup> SSM is the second most common subtype of melanoma in SCI and it occurs more in women.<sup>[5]</sup> NM, the third most common melanoma in SCI, occurs more in men than women.<sup>[5,45,46]</sup> LMM is the least common melanoma in SCI.<sup>[2,14]</sup> This is most probably due to melanin protection from UVR of the skin in this group of people as LMM occurs on sun-damaged skin, especially of the face.<sup>[47]</sup>

## GENETICS OF MELANOMA

Melanomas arise from different molecular pathways with the different subtypes of melanoma associated with different genetic mutations.<sup>[47,48]</sup> The molecular pathways that have been

reported in CMM are Cyclin D1, Neuroblastoma RAS (NRAS), and BRAF, Cyclin-dependent kinase inhibitor 2A (CDKN2A), Melanocortin 1 receptor (MC1R), and Kit-ligand (C-kit).<sup>[48-51]</sup>

Several studies have been conducted on the genetics of CMM in Caucasians but not many specifically with SCI.<sup>[52]</sup> This is due to the low incidence of melanoma in this group of people and consequently, too few people for the study. SCIs have a low incidence of gene mutation, further enhancing the theory that melanoma in SCI has different pathogenesis from melanoma in Caucasians.<sup>[52]</sup> Given that the risk factors for and subtypes of melanoma in SCI are different from those in Caucasians, genetic mutations may also differ.

Cyclin D1 amplification occurs early and is said to play a role in the genesis of cutaneous melanoma, especially in ALM compared to other melanomas and this is independent of the presence or absence of p16 mutation.<sup>[49]</sup> Another gene mutation associated with ALM is c-kit.<sup>[50]</sup> Kit mutation is found mainly in metastatic acral and mucosal melanomas.<sup>[50]</sup> Kit-ligand is a stem cell factor required by melanocytes for development and maintenance. Loss of kit expression is associated with high metastatic potential.<sup>[50]</sup>

NRAS and BRAF mutations occur early in melanocytic lesions as these mutations are found in naevi.<sup>[48]</sup> This mutation is associated with melanomas on nonchronic sun-damaged skin.<sup>[53]</sup> Thus mutations of BRAF and NRAS are found to be low in ALM the commonest melanoma in SCI which is not associated with sun exposure. Thus BRAF mutation is not expected to be high and may not be found in SCI.

In a study of 26 SCI with melanoma, 2 BRAF mutations were found and these were different from the V600E mutation in Caucasians.<sup>[52]</sup> In the same study, 3 NRAS mutations were found on exon 1 in SCI, and this was different from what is observed in Caucasians in whom the mutation is on exon 2.<sup>[52]</sup>

CDKN2A encodes two growth inhibitors; p16 and alternative reading frame (ARF).<sup>[54]</sup> The p16-ARF is required by melanocytes for senescence and pigmentation. Melanoma genesis requires the melanocytes to overcome senescence, which is the normal progression of a benign naevus.<sup>[54]</sup> A study of 32 ALM revealed that there was no loss of p16 in ALM.<sup>[55]</sup> Hence, loss of p16 is not associated with ALM.

MC1R is involved in both pigment production and melanoma genesis.<sup>[51]</sup> The presence of multiple MC1R variants is associated with a risk of developing melanoma, especially at an early age because MC1R variants increase the penetrance of CDKN2A. In ALM, the subtype of melanoma most encountered in SCI, MC1R variants are low.<sup>[56]</sup>

In summary, gene mutation does occur in ALM, the most common subtype of melanoma in SCI. The relevant gene mutations in ALM are CD1 and c-kit. The other genes found to be mutated in melanomas (BRAF, p16, MC1R) have a low occurrence in ALM and thus may not be relevant in SCI.

In conclusion, melanoma, although rare does occur in SCI.

Most of the studies on cutaneous melanoma are from the Caucasian population with a resultant lack of details on the characteristics and peculiarities of cutaneous melanoma in SCI. The low incidence of melanoma in SCI is irrespective of geographical location and attributed to the protective effect of melanin. In SCI, the incidence of melanoma varies between males and females and also varies with age, with melanoma occurring more in males.

Sun exposure and trauma have not been found to be risk factors in SCI. Preexisting melanocytic nevi may be a risk factor for melanoma in SCI, especially ALM. The most common anatomic sites of melanoma occurrence in SCI is subungual and acral. Female SCI have melanomas only on their lower limbs, unlike their male counterparts who have melanomas not only on their lower limbs but also on other parts of their bodies.

There are some observed differences in melanoma between SCI and Caucasians. Melanoma is diagnosed almost a decade later in SCI compared to Caucasians. The risk factors for melanoma in SCI are not as well-known as in Caucasians. Melanoma is truncal in Caucasians and acral in SCI. Melanoma specific 5-year survival is poor in SCI due to advanced, ulcerated lesions at presentation and low perception of the risk of melanoma both by physicians and patients. The genetics of melanoma has not been well studied in SCIs. For now, genetic mutations are inferred from studies carried out on Caucasians.

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