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Original article

Epidemiology of cutaneous malignant melanoma in Reunion Island

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ABSTRACT

Introduction: The incidence of cutaneous malignant melanoma (CMM) is increasing worldwide. The aim of this study was to evaluate the epidemiology of CMM in Reunion Island, a French overseas department whose population is characterized by high ethnic diversity and high exposure to ultraviolet radiation.
Methods: This cross-sectional study examined all cases of in situ CMM and invasive CMM diagnosed between 1 January and 31 December 2015 in the Reunionese population.
Results: One hundred and three new cases of CMM were recorded in Reunion Island in 2015: 33 cases of in situ CMM and 70 cases of invasive CMM. The sex ratio of men to women was 1.3 and 80% of patients had a fair skin phototype (Fitzpatrick skin phototype ≤ III). Age-standardized incidence rates of invasive CMM for all skin phototypes combined were 6.7/100,000 person-years (PY) in women and 5.3/100,000 PY in men. Crude incidence rates of invasive CMM for fair skin phototypes were estimated to be over 21/100,000 PY in women and over 25/100,000 PY in men.
Conclusions: In Reunion Island, the incidence of CMM in the population with fair skin phototype is very high. Primary and secondary prevention measures should be reinforced and tailored to the local context.

1. Abbreviations

ASIR	Age-standardized incidence rate
CIR	Crude incidence rate
CMM	Cutaneous malignant melanoma
PSSM	Palms, soles and subungual melanoma
PY	Person-Years
SIR	Standardized incidence ratio
UV	Ultraviolet
95% CI	95% Confidence Interval

2. Introduction

Over the past 50 years, the incidence of cutaneous malignant melanoma (CMM) has been steadily increasing, predominantly in Caucasian populations around the world. The phenomenon is such that some authors now speak of an "epidemic" [1]. The highest age-standardized incidence rates (ASIR, world standard population) of invasive CMM are observed in New Zealand and Australia, where they exceed 30/100,000 person-years (PY) [2,3]. The next highest ASIR are found in the United States, Northern Europe, and Switzerland, where they vary between 20/100,000 PY and 25/100,000 PY. Rates of ASIR observed in metropolitan France are lower: in 2015, they were estimated at 13.6/100,000 PY in men and 13.5/100,000 PY in women [4].

This sharp increase in the incidence of CMM in predominantly Caucasian populations is associated with increased early diagnosis and with increased exposure to solar radiation, with exposure to ultraviolet (UV) radiation being one of the main risk factors along with skin phototype [1,5–7]. Reunion Island is a French overseas department located near the equator and characterized by high annual sunshine levels. The Universal UV Index is usually above 8 in seaside areas; it easily exceeds 10 in the summer (extreme exposure) and even 15 at high altitudes. The population of Reunion Island is very ethnically diverse since it is composed of multiple communities that settled on the island during the different stages of colonization. Although ethnic censuses are forbidden in France,

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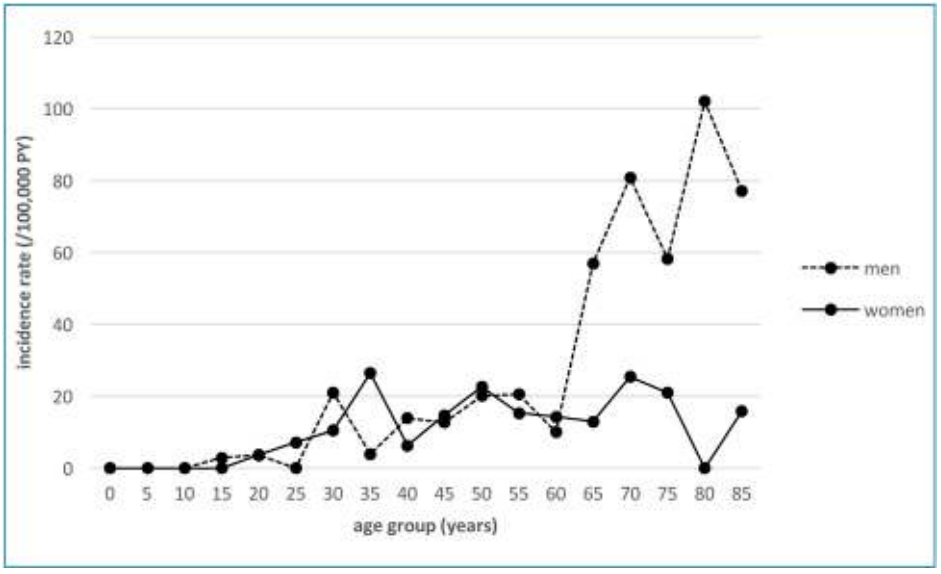

Fig. 1. Age-specific incidence rates. Reunion Island 2015 ($N = 98$).

approximate estimates of population distribution by community are available. Thus, "Cafres" (Reunionese of African origin) are estimated to represent 40 to 50% of the population of Reunion Island, "Malbars" (Tamil Indians) 22 to 27% of the population, Yabs (white Creoles) 15% of the population, "Zoreils" (Reunionese originating from metropolitan France) 9 to 11% of the population, "Chinese" 3% of the population, "Zarabes" (Muslim Indians) 3% of the population, and other communities (Mahorais, Comorians, Malagasy, etc.) 4 to 6% of the population. All skin phototypes are then significantly represented on the island, including those that have a high risk of developing skin tumors. To date, however, no study has attempted to estimate the risk of CMM in the Reunionese population. The aim of this study was to evaluate the epidemiology of CMM in Reunion Island, in terms of incidence, clinical and histopathological characteristics.

3. Patients and methods

3.1. Population

The data were collected by the Reunion Island Cancer Registry, a population-based registry that records all incident cases of malignant tumors in Reunion Island, in accordance with international recommendations (International Agency for Research on Cancer, European Network of Cancer Registries, French Network of Cancer Registries) [8,9]. To ensure completeness, case identification and data collection are active, in histopathology laboratories, public hospitals, private clinics, the regional cancer network and the social security database. Our study examined all cases of in situ CMM and invasive CMM diagnosed between 1 January and 31 December 2015 in the Reunionese population (i.e. individuals residing in Reunion Island at the time of diagnosis). Socio-demographic data, residence area, risk factors for skin tumors and CMM clinicopathological features were collected retrospectively for all patients by their dermatologist. Cases of mucosal or ocular melanomas were excluded from the study. Registry procedures were approved by the French National Commission for Data Protection and Liberties (CNIL authorization no. 909471).

3.2. Methods

Annual incidence rates were calculated using INSEE (Institute of Statistics and Economic Studies) population estimates as of 1 January 2015, available by sex, by 5-year age group and by region [10]. They were expressed per 100,000 PY. Age-standardized incidence rates were calculated with their 95% confidence interval (95% CI) using the world standard population [11]. For comparison purposes and in accordance with international recommendations for the publication of cancer incidence data, incidence rates were calculated for patients diagnosed with a first invasive CMM in 2015 [12]. The island is divided into 4 administrative regions - North, East, West and South–with these regions differing from each other in terms of their climatic conditions and the socio-demographic characteristics of their populations. In order to compare the incidence of the 4 regions taking into account possible differences in age distributions between the populations, standardized incidence ratios (SIR) were calculated for each region of residence using age-specific incidence rates estimated for the entire island. Crude incidence rates (CIR) of invasive CMM for fair-skinned phototypes (Fitzpatrick skin phototypes $\leq$ III) were calculated with estimations of the Reunionese population with fair skin phototype as the denominator [13]. These estimations were based on the estimates of population distribution by community that are available, ethnic statistics being prohibited in France by law 78-17 on *Information Technology and Freedom* of January 6, 1978. Thus, we have made 2 hypotheses regarding the proportions of the Reunionese population with fair skin phototype: a low hypothesis taking the percentage of the Reunionese population with fair skin phototype for both sexes as 24% (9% of metropolitan origin and 15% white Creoles) and a high hypothesis taking the percentage of the Reunionese population with a fair skin phototype for both sexes as 29% (11% of metropolitan origin, 3% of Chinese origin, and 15% white Creoles).

Qualitative variables were expressed as numbers and percentages, and quantitative variables were expressed as medians with 25th and 75th percentiles (p25; p75). Percentages were compared using the Chi^2 test or Fisher's exact test, as appropriate. Continuous variables were compared using Student's *t*-test or the Wilcoxon test, as appropriate. Hypotheses were tested with an alpha risk of 0.05, and 95% confidence intervals were calculated. All statistical analyses were performed using STATA SE V16® software (StataCorp, Texas).

4. Results

In 2015, 103 new cases of CMM in 98 patients were recorded in Reunion Island, including 33 cases of in situ CMM (32%) and 70 cases

Table 1
Clinicopathological characteristics of patients at CMM diagnosis. Reunion Island 2015 ($N = 103$).

	Women ($N = 45$)	Men ($N = 58$)	Total ($N = 103$)	P
Age (years), median (p25–p75)	49 (36;56)	60 (45;72)	53 (44;69)	7.10^{-3}
Tumor location, *n* (%)				
Limbs[a]	23 (51.1)	19 (32.8)	42 (40.8)	
Trunk	15 (33.3)	27 (46.6)	42 (40.8)	
Head and neck	3 (6.7)	8 (13.8)	11 (10.7)	
Palms, soles and subungueal	4 (8.9)	4 (6.9)	8 (7.8)	0.2
Pathology, *n* (%)				
In situ CMM ($n = 33$)				
SSM	7 (53.9)	12 (60.0)	19 (57.6)	
Lentigo maligna	3 (23.1)	7 (35.0)	10 (30.3)	
Acro-lentiginous	2 (15.4)	0 (0.0)	2 (6.1)	
Unclassifiable	1 (7.7)	1 (5.0)	2 (6.1)	0.4
Invasive CMM ($n = 70$)				
SSM	26 (81.3)	27 (71.1)	53 (75.7)	
Nodular	3 (9.4)	3 (7.9)	6 (8.6)	
Acro-lentiginous	1 (3.1)	3 (7.9)	4 (5.7)	
Spitzoid	1 (3.1)	1 (2.6)	2 (2.9)	
Unclassifiable	1 (3.1)	4 (10.5)	5 (7.1)	0.7
Breslow thickness[b](mm)				
< 0.8	19 (59.4)	24 (63.2)	43 (61.4)	
≥ 0.8 and < 1.0	3 (9.4)	4 (10.5)	7 (10.0)	
≥ 1.0 and < 2.0	6 (18.8)	2 (5.3)	8 (11.4)	
≥ 2.0 and < 4.0	1 (3.1)	3 (7.9)	4 (5.7)	
≥ 4.0	3 (9.4)	3 (7.9)	6 (8.6)	
NS	*0 (0.0)*	*2 (5.3)*	*2 (2.9)*	0.5[d]
Ulceration[b]				
Yes	3 (9.4)	3 (7.9)	6 (8.6)	
No	27 (84.4)	33 (86.8)	60 (85.7)	
NS	2 (6.3)	2 (5.3)	4 (5.7)	1.0[d]
AJCC stage[c]				
0	13 (28.9)	20 (34.5)	33 (32.0)	
I	26 (57.8)	26 (44.8)	52 (50.5)	
II	4 (8.9)	4 (6.9)	8 (7.8)	
III	0 (0.0)	2 (3.5)	2 (1.9)	
IV	0 (0.0)	2 (3.5)	2 (1.9)	
NS	2 (4.4)	4 (6.9)	6 (5.8)	0.4[d]

NS: Not specified; CMM: Cutaneous malignant melanoma; p25: 25th percentile; p75: 75th percentile; SSM: Superficial spreading melanoma.
[a] excluding palms, soles and subungual locations.
[b] concerns only the 70 invasive CMMs.
[c] as defined in the 8th edition of the AJCC.
[d] Cases with non-specified data were excluded from comparisons.

of invasive CMM (68%). The sex ratio of men to women was 1.3. Median age at diagnosis was 53 years (p25 = 44.0; p75 = 69.0); it was lower in women (49 years (p25 = 36.0; p25 = 56.0)) than in men (60 years (p25 = 45.0; p75 = 72.0); $P = 7.10^{-3}$). The overrepresentation of men was observed in all age groups aged over 65 years (Fig. 1). Of the 98 patients diagnosed with CMM in 2015, 45 (45.9%) were born in metropolitan France and 48 (49%) resided in the western part of Reunion Island; the proportion of patients born in metropolitan France ranged from 26.7% in the southern part of Reunion to 58.3% in the western part. The distribution of skin phototypes was: 55 (56.1%) patients with skin phototype I or II (60 tumors), 23 (23.5%) patients with skin phototype III (23 tumors) and 15 (15.3%) patients with skin phototype IV, V, or VI (15 tumors); data was missing for 5 (6.1%) patients (5 tumors). Four patients had 2 or 3 CMM diagnosed in 2015. All of them had type I or II skin phototype, and the diagnoses were synchronous for 2 of them and metachronous for the 2 others.

Superficial spreading melanoma was the most common CMM ($N = 72$; 69.9%). Tumors were more frequently located on the limbs (excluding palms, soles and subungual melanomas (PSSM)) in women (51.3% vs. 34.5% for men; $P = 0.05$) (Table 1). Tumors of the limbs, trunk and PSSM were more often invasive CMM [$N = 32$ (76.2%), $N = 28$ (66.7%) and $N = 6$ (75.0%), respectively], whereas tumors of the head and neck were more often in situ CMM [$N = 7$ (63.6%)] ($P = 0.03$); 6 of the 7 in situ tumors of the head and neck were lentigo maligna. The median age at diagnosis was 69 years (p25 = 51.0; p75 = 76.0) for head-and-neck tumors, 69.5 years (p25 = 43.5; p75 = 78.5) for PSSM and, 51 years (p25 = 40.5; p75 = 66.0) for tumors on the trunk and limbs ($P = 0.03$). The median Breslow thickness of invasive CMM was 0.63 mm (p25 = 0.35; p75 = 1.03) and varied significantly according to tumor location, from 0.46 mm in tumors of the trunk to 2.9 mm in PSSM ($P = 3.10^{-3}$).

Melanomas on palms and soles and subungual melanomas accounted for 40% ($N = 6$) of tumors in patients with skin phototype ≥ IV (Table 2). The proportions of invasive tumors were similar in patients with skin phototype ≥ IV ($N = 9$; 60.0%) and in patients with skin phototype ≤ III ($N = 57$; 68.7%) ($P = 0.5$), but the median Breslow thickness was higher for invasive CMM in patients with skin phototype ≥ IV [1.9 mm (p25 = 0.5; p75 = 4.1)] than in patients with skin phototype ≤ III (0.7 mm (p25 = 0.4; p75 = 0.9); $P = 0.06$). Lastly, patients with skin phototype ≥ IV were more likely to have acro-lentiginous melanoma ($N = 5$; 33.3%) than patients with skin phototype ≤ III ($N = 1$ (1.2%); $P < 1.10^{-3}$); 5 of the 6 acro-lentiginous melanomas were located on the feet, and 2 were in situ. Among the 4 invasive acro-lentiginous melanomas, 3 had a Breslow thickness greater than 2 mm (missing for the fourth).

Among the 70 invasive CMM diagnosed in 2015, 6 concerned patients with a history of CMM diagnosed before 2015 and 2 concerned one patient. Incidence rates were therefore calculated for the 63 patients diagnosed with a first invasive CMM in 2015 (35 men and 23 women). CIR were 8.5/100,000 PY (95% CI: 5.7–11.3) in men and 6.4/100,000 PY (95% CI: 4.0-8.8) in women. ASIR were

Table 2
Clinicopathological characteristics of patients at CMM diagnosis according to phototype. Reunion Island 2015 ($N = 98$)[a].

	phototype ≤ III ($N = 83$)	phototype ≥ IV ($N = 15$)	p
Tumor location, n (%)			$< 1.10^{-3}$
Limbs[b]	36 (43.4)	3 (20.0)	
Trunk	35 (42.2)	6 (40.0)	
Head and neck	11 (13.3)	0 (0.0)	
Palms, soles and subungual	1 (1.2)	6 (40.0)	
Pathology, n (%)			
In situ CMM ($n = 32$)			0.08
SSM	15 (57.7)	3 (50.0)	
Lentigo maligna	9 (34.6)	1 (16.7)	
Acro-lentiginous	0 (0.0)	2 (33.3)	
Unclassifiable	2 (7.7)	0 (0.0)	
Invasive CMM ($N = 66$)			9.10^{-3}
SSM	47 (82.5)	4 (44.4)	
Nodular	4 (7.0)	2 (22.2)	
Acro-lentiginous	1 (1.8)	3 (33.3)	
Spitzoid	2 (3.5)	0 (0.0)	
Unclassifiable	3 (5.3)	0 (0.0)	
Breslow thickness[c] (mm) median (p25; p75)	0.65 (0.35; 0.90)	1.9 (0.48;4.10)	0.06
AJCC stage[d]			9.10^{-3}[e]
0	26 (31.3)	6 (40.0)	
I	47 (56.6)	3 (20.0)	
II	5 (6.0)	3 (20.0)	
III	1 (1.2)	1 (6.7)	
IV	0 (0.0)	1 (6.7)	
NS	4 (4.8)	1 (6.7)	

NS: Not specified; CMM: Cutaneous malignant melanoma; p25: 25th percentile; p75: 75th percentile; SSM: Superficial spreading melanoma.
[a] 98 CMMs with phototype information.
[b] excluding palms, soles and subungual locations.
[c] concerns only the 66 invasive CMMs, one missing data for patients with phototype ≥ IV.
[d] as defined in the 8th edition of the AJCC.
[e] Cases with non-specified data were excluded from comparisons.

Table 3
Age-standardized incidence rate and standardized incidence ratios by sex and region of residence, Reunion Island 2015 ($N = 63$).

Region of residence	Men			Women			Total		
	N (%)	ASIR[a] (95% CI)[b]	SIR[c] (95% CI)[b]	N (%)	ASIR[a] (95% CI)[b]	SIR[c] (95% CI)[b]	N (%)	ASIR[a] (95% CI)[b]	SIR[c] (95% CI)[b]
North	5 (14)	4.5 [0.5–8.5]	0.68 [0.22–1.60]	5 (18)	4.8 [0.6–9.1]	0.82 [0.27–1.91]	10 (16)	4.7 [1.7–7.7]	0.74 [0.36–1.36]
South	11 (31)	5.6 [2.2–9.0]	0.85 [0.42–1.51]	9 (32)	4.2 [1.4–7.0]	0.89 [0.41–1.69]	20 (32)	4.9 [2.7–7.1]	0.87 [0.53–1.34]
West	16 (46)	11.8 [6.0–17.6]	1.80 [1.03–2.92]	12 (43)	9.1 [3.8–14.4]	1.71 [0.89–2.99]	28 (44)	10.4 [6.4–14.3]	1.76 [1.17–2.55]
East	3 (9)	4.2 [0.0–9.0]	0.52 [0.11–1.51]	2 (7)	2.2[0.0–5.2]	0.42 [0.05–1.50]	5 (8)	2.9 [0.3–5.5]	0.48 [0.15–1.11]
Total	35 (100)	6.7 [4.4–8.9]	Ref	28 (100)	5.3 [3.3–7.3]	Ref	63 (100)	5.9 [4.4–7.4]	Ref

[a] ASIR: Age-standardized incidence rate.
[b] 95% CI: 95% confidence interval.
[c] SIR: Standardized incidence ratio.

6.7/100,000 PY (95% CI: 4.4–8.9) in men and 5.3/100,000 PY (95% CI: 3.3–7.3) in women. They showed significant heterogeneity according to region of residence (Table 3), ranging from 2.2/100,000 PY for women residing in the east part of the island, to 11.8/100,000 PY for men residing in the west region of the island. Thus, the standardized incidence ratio for both sexes in the western region was 1.76 (95% CI: 1.17–2.55).

The mean estimated CIR of invasive CMM for skin phototypes ≤ III was 27.8/100,000 PY in men (low hypothesis = 25.1/100,000 PY; high hypothesis = 30.4/100,000 PY) and 23.4/100,000 PY in women (low hypothesis = 21.2/100,000 PY; high hypothesis = 25.6/100,000 PY).

5. Discussion

One hundred and three new cases of CMM were recorded in 2015 in Reunion Island, 33 cases of in situ CMM and 70 cases of invasive CMM. The ASIR of invasive CMM observed in Reunion Island were 6.7/100,000 PY in men and 5.3/100,000 PY in women for all skin phototypes combined. They were lower than those reported in metropolitan France (13.6/100,000 PY in men and 13.5/100,000 PY in women in 2015); they were also lower than those reported in most Western countries, namely Northern and Western European countries, the US, Canada, Australia and New Zealand (generally above 10/100,000 PY) [3,4]. The low incidence rates observed in Reunion compared to metropolitan France were probably largely related to the fact that less than 30% of Reunionese have a phototype at high risk of CMM (skin phototype ≤ III). Thus, 45% of the CMM diagnosed in Reunion in 2015 concerned people born in mainland France, whereas these people represent about 10% of the Reunion Island population. Screening practices may also explain these low levels of invasive CMM, allowing earlier diagnosis and increasing the proportion of CMM diagnosed at the in situ stage. Indeed, many studies have shown that the increase in CMM incidence in recent decades has been significantly higher for in situ CMM than for invasive CMM, mainly due to screening [14–17]. Thus, the proportion of in situ CMM among all CMM in a population provides an indication on the importance of screening in this population. According to various studies, the proportions of in situ CMM ranged from 17% for the 2008–2012 period in Denmark to 44.4% in 2013 for the SEER program registries and 54% in 2015 in Australia (State of Victoria) [15,16]. In Reunion Island, the proportion of in situ CMM was 32% in 2015, which is quite close to the proportion of 25% described in 18

European cancer registries for the period 1995-2012 [17]. Finally, given that the Reunion registry uses the same information sources and registration procedures as do other French registries, the low incidence rates observed in Reunion compared to mainland France do not appear to be attributable to a lack of exhaustivity of case registration.

The ASIR of invasive CMM in Reunion Island were higher than those reported in the French overseas departments of the Americas (French West Indies and Guyana), where they ranged from 2.2 to 3.8/100,000 PY in men and from 1.1 to 3.3/100,000 PY in women for the period 2007–2016 [18]. However, they were lower than those observed in New Caledonia (a French overseas territory located in the South Pacific Ocean), where they were 10.3/100,000 PY in men and 7.1/100,000 PY in women in 2015 [19]. Interpreting the differences in ASIR between the various French overseas departments, which are all located at latitudes with potentially high UV exposure, is difficult, as it requires taking into account the proportion of inhabitants with fair skin phototype in each department. Indeed, we observed significant differences in ASIR according to region of residence in Reunion Island, despite the low number of CMM cases recorded in each of the regions (especially in the Eastern region). The ASIR of invasive CMM were high in the western part of the island, which is characterized by many beaches, less rain and less windy weather and has the highest proportion of inhabitants originating from metropolitan France compared to other regions, particularly the eastern region. Likewise, the CIR of invasive CMM for fair skin phototypes were quite high, estimated to be over 21/100,000 PY in women and over 25/100,000 PY in men. These CIR should be interpreted with caution—especially for comparison purposes—because they are not age-standardized and because they are based on a hypothetical percentage of the Reunionese population with fair skin phototype due to the ban on ethnic statistics in France. Nevertheless, they are much higher than those reported in the general population. Apart from the proportion of inhabitants with fair skin phototype, the differences in incidence observed between the 4 regions of the island may be due in part to the provision of care, notably via screening [20,21]. Indeed, the majority of dermatologists on the island work in the western and southern regions.

The incidence of invasive melanomas was higher in men than in women from the age of 65. Moreover, we observed sex-specific differences in the distributions according to tumor location: women had a higher proportion of CMM located on the limbs while men more frequently had CMM located on the trunk or the head and neck. These gender differences have already been described in other populations, as shown in the study by Olsen CM et al. that concerned eight Caucasian populations [22]. In addition, our study found differences in disease presentation at diagnosis according to tumor location. Tumors of the limbs and trunk were mostly invasive CMM and were diagnosed around the age of 50. By contrast, tumors of the head and neck, which were less common, were mostly in situ CMM and were diagnosed at older ages. These findings are consistent with studies that have identified differences in cancer pathways according to histology, sun exposure, age at diagnosis and tumor location. Thus, a distinction has been made between superficial spreading melanoma, which is allegedly caused by intermittent UV exposure, located on covered parts of the body, and observed at early ages, and lentigo maligna, which is presumably caused by chronic UV exposure, located on uncovered parts of the body and observed at later ages [23–26].

Dark-skinned patients were more likely to have acro-lentiginous melanoma. Acro-lentiginous melanoma is a type of CMM located on the palms or soles or beneath the nail. Acro-lentiginous melanoma are not associated with sun exposure: it is rare in fair-skinned populations, but can account for 20-70% of CMM in darker-skinned populations [24,27–29]. In our study, 6 acro-lentiginous melanomas were diagnosed in 2015 (5.8% of all CMM), 5 in patients with a phototype ≥ 4 (33.3% of CMM diagnosed in patients with a phototype ≥ 4). As described in the literature, they were predominantly located on the feet.

Lastly, the median Breslow thickness was significantly higher in patients with skin phototype $\geq$ IV than in patients with skin phototype $\leq$ III for invasive CMM. These differences between fair-skinned and dark-skinned populations have already been described in previous studies, as in the West Indies and Guyana [24,30–33]. There are several reasons that may explain the late diagnosis of CMM in darker-skinned populations. The main ones are certainly lack of awareness of the risk of CMM among dark-skinned patients and their physicians, and the fact that these diagnoses are more difficult in these populations [27,31].

In conclusion, the incidence of CMM in at-risk populations on Reunion Island is close to that observed in countries with high incidence rates. This finding reflects the multifactorial aspect of this disease, which stems from a mixture of environmental and individual factors. Accordingly, medical demography and prevention measures against UV exposure should be reinforced in all areas (especially schools and workplaces in daily life – see http://www.missionsoleilreunion.com) – and should be adapted to the local context. Moreover, as dark-skinned populations are more likely to have advanced diseases, it seems important to improve the awareness of these populations and of physicians.

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Disclosure of interest

The authors declare that they have no competing interest.

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