Masterthesis

Clinical and dermoscopic findings of cutaneous melanoma depending on skin phototype and other pigmentary traits

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Statutory declaration

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Abstract

Introduction: According to recent publications, pigmentary traits influence the appearance of both benign and malignant melanocytic tumours.

Objective: Our aim was to assess how Fitzpatrick's skin type and other pigmentary traits influenced the clinical and dermoscopic signs of melanoma in a clinical setting.

Methods: This was a retrospective study of consecutive cases of melanoma from the Hospital General de Valencia (HGUV) in Valencia, Spain between 2008 and 2013. Age and sex, phototype, hair and eyes colour, localization and diameter of the lesion were collected. Cases missing a good clinical and/or dermoscopic image or some of these clinical parameters were excluded. In regards to histology, we registered Breslow and mitotic indexes and subtype of melanoma (superficial spreading melanoma, SSM; lentigo maligna melanoma, LMM; nodular melanoma, NM, and acral lentiginous melanoma, ALM). Dermoscopic analysis was performed according to the International Dermoscopy Society Consensus. Bivariate and multivariate analyses were carried out.

Results: We included a total of 171 cases, 99 in males (57,9%) and 72 in females (42,1%). Men were slightly older (63,1 vs 61,5 yo, respectively). SSM was the most frequent histologic subtype and the trunk the most frequent location in both sexes. Women presented more often with lesions located on the lower limbs (22,2% *vs* 8,1% in males, p = 0,009), whereas men exhibited a higher proportion of melanomas on the head and neck region (26,3% *vs* 12,5% in females, p = 0,028). Lesion diameter, Breslow and mitotic indexes were tightly related to histologic subtype. Tan individuals were older at diagnosis (66,3 *vs* 59,8 years for sensitive-skinned, p = 0,017) and presented more frequently with LMM (29,3% in tan individuals *vs* 8,3% in sensitive, p = 0,014). NM was in turn more frequent in sensitive-skinned individuals. Regarding dermoscopy, colour dark brown was more often seen in tan-skinned individuals and milky red areas, more often on sensitive skin. In the multivariate analysis, tan individuals had an odds ratio (OR) for having dark brown in their lesions of 4,434 whereas red was more often seen in sensitive skin (OR of 2,412). Finally, a sensitive-skin type, red/blond hair and blue/green

eyes were all positive predictors for the presence of milky-red areas with an OR of 2,962, 3,503 and 3,091, respectively.

Conclusions: This study shows how, in a routine, clinical setting, pigmentary traits may influence the clinical and dermoscopic appearance of melanomas regardless of histologic correlates. This is in accordance with previous studies in which genetic markers for sun sensitivity were used. In addition, LMM was remarkably more frequent in darker skinned individuals whereas nodular melanoma showed a tendency towards a higher incidence in sensitive-skinned patients. Multicentre studies with higher numbers are needed to confirm these findings.

Introduction

In order to prevent and favour early diagnosis of melanoma, the influence of phenotypic characteristics and people's habits - basically related to ultraviolet exposure - has been extensively studied. Sun-sensitivity and fair skin, along with light hair and eyes colour, are among the most important risk factors.[1-9] Evidence suggests that, in addition, these phenotypic traits have an effect on the clinical examination, as dermoscopic characteristics of benign melanocytic nevi are influenced by skin type. In Caucasians, Fitzpatrick's skin type I tend to develop large (> 5mm) nevi with light-brown coloration, reticular pattern, and central hypopigmentation, whereas patients with skin type IV tend to show small (< 5mm) dark brown lesions with a central hyperpigmentation (see Figure 1).[10] People with skin phototype V often exhibit a dark brown reticular pattern and type VI individuals present with structureless lesions, often exhibiting black, blue and grey colours.[11,12]

Pigmentary traits have been found to influence clinical and dermoscopic findings in melanomas too. Patients with oculocutanous albinism, who exhibit nevi similar to skin type I patients,[13] rarely develop melanomas, but when they do, they are often nodular amelanotic tumors.[14] A few years ago, "white" dysplastic nevi were described in association with amelanotic melanomas in a few fair-skinned individuals.[15,16] More recently, Cuéllar et al.[17] showed in a short series of 9 patients from families carrying CDKN2A mutations that polymorphisms in the melanocortin receptor 1 (MC1R) conferring the so-called "red hair" phenotype (RHC phenotype) determined the development of melanomas exhibiting fewer colours and structures evaluated with the ABCD dermoscopy algorithm and were often detected due to subtle changes in digital follow-up.[17] Subsequently, a larger cohort study of patients from CDKNA mutated families yielded similar results in their nevi but was inconclusive regarding their 21 melanomas.[18]

Farignoli et al. recently correlated for the first time MC1R variants and dermoscopic findings in a larger number of patients with sporadic melanomas.[19] They analysed 64 lesions, including only superficial spreading and nodular

melanomas. They did not include lentigo maligna melanoma and acral lentiginous melanomas. In line with Cuéllar et al., melanomas in patients carrying MC1R polymorphisms had a lower Total Dermoscopy Score using the ABCD algorithm. An atypical pigment network was prevalent in non-carriers of MC1R variants, dark skinned and haired patients, who developed melanomas of the superficial spreading type. In turn, patients with fair skin and light hair and eye colour developed thicker melanomas, mainly of the nodular type, exhibiting an atypical vascular pattern.

Since pigmentary traits may modulate what looks clinically benign and what appears suspicious in a given individual, the dermatologist should be able to adapt the criteria for excision. In lighter skin types, the tendency towards melanocytic tumours, both malignant and benign, with fewer colours, may hinder their early diagnosis. In turn, the presence of very pigmented lesions in darker skin types (the so-called hypermelanotic nevi) may cause concern and prompt unnecessary excisions.

Our aim was to investigate the associations between sun-sensitivity (Fitzpatrick's skin phototype), hair and eyes colour and the clinical and dermoscopic findings in melanoma in a routine clinical setting.

Materials and methods

Patient selection and design

This was a retrospective study of consecutive cases of histopathologically diagnosed melanoma at the Hospital General de Valencia (HGUV) in Spain between 2008 and 2013. This is a tertiary hospital covering the southern part of the city of Valencia and some additional rural areas with total 370 946 inhabitants. In addition, some patients are referred after diagnosis of melanoma stage IIB to IV from other hospitals in surrounding areas.

We included only cases from which good clinical and dermoscopic images were available and collected the following clinical data for each patient: age and sex, phototype according to Fitzpatrick's classification, hair and eyes colour, localization and diameter of the lesion. When a suspicious lesion was encountered in their daily routine, the dermatologist or resident in charge of the patient took the clinical images using compact cameras with consent of the patient (see acknowledgments). Hand-held non-contact polarized dermoscopes (DermLite II Pro HR and DermLite DL3) were attached to these cameras in order to obtain dermoscopic images. In some thick, vascularised tumours, ultrasound gel was used between the lesion and the dermatoscope.

For this study, only three histologic parameters were assessed: Breslow thickness, mitotic index (mitosis/mm^2) and subtype of melanoma according to Clark's classification: superficial spreading (SSM), nodular (NM), lentigo maligna (LMM) and acral lentiginous (ALM). Mitotic index was calculated only for invasive lesions.

Dermoscopic analysis

Dermoscopic description was according to the International Dermoscopy Society's Consensus previously published.[20] The images were analysed by two investigators (Juan Garcias-Ladaria, Iris Zalaudek) blinded for the patients demographics or melanoma-related histopathological criteria. Six colours were assessed according

to the ABCD algorithm of dermoscopy: white, red, light brown, dark brown, black and blue-grey. Colours and structures recorded are summarized in table 1 (see appendix).

Statistical analysis

Statistical analysis was carried out using Wizard pro® 1.7.15 for Mac OS X. Bivariate analysis was performed using the chi-square test for qualitative variables. Binomial variables (presence/absence, yes/no) were compared using the z-score. Quantitative parameters between two categories where compared using the t-test. The ANOVA test was used when more than two groups were compared (e. g. Breslow thickness between histologic subtypes).

For multivariate analysis, a linear regression model controlling possible confounding variables was constructed in order to obtain odds ratios for significant variables predicting dermoscopic differences between skin phototypes.

Significant differences were considered when p score was < 0.05.

Results

General Data. Clinical, dermoscopic and pathologic correlates

From January 2008 to December 2013, 602 new patients with melanoma were seen in the HGUV (316 males, 286 females). The most frequent exclusion criterion was a missing or a bad quality clinical and/or dermoscopic image. In around one third of the patients, the information regarding phototype and pigmentary traits was not recorded. One patient had two melanomas, making out a sample of 171 lesions included in the study, of which 126 (73.7%) were invasive.

We included 99 cases in males (57.9%) and 72 lesions in females (42.1%). Histologic subtypes, localization, average diameter, Breslow and Mitotic indexes for both groups are presented in table 2. Men were slightly older and presented with larger diameters, higher Breslow and mitotic indexes but these differences did not reach statistical significance. The trunk was the most frequent localization in both males and females. However, women presented with a larger proportion of lesions located on the limbs, especially the lower limbs (22.2% *vs* 8.1% in males, p = 0.009), whereas head and neck was more often affected in men (26.3% *vs* 12.5% in females, p = 0.028).

The most frequent histologic subtype was SSM (n = 116) accounting for the 70.3% of the lesions in men and the 63.9% in women. LMM was the second frequent histologic type (n = 40), making out 25.3% in males and 20.8% in females. Only eight (4.7%) NM and seven (4.1%) ALM were included. Histologic variants determined the presence of some features in dermoscopy. Left aside the signs of ALM and LMM due to their specific anatomic location, ALM showed more often ulceration than the other types (50% *vs* 12.3% respectively, p = 0.002, see figure 2). NM correlated also with dermoscopic ulceration (42.9% *vs* 12.8% for other variants, p = 0.025) and milky-red areas (58.1% *vs* 18.3% for other histologic subtypes, p = 0,011, see figure 3). LMM exhibited the colour light brown more often than other variants (97.5% vs 76.3% respectively, p = 0.002, see figure 4). Finally, compared with the other subtypes, SSM presented more often with colours dark

brown (94.8% in SSM *vs* 78.2% respecticely, p < 0.001) and black (83.6% *vs* 58.2%, p < 0.001). Structures significantly associated with SSM were irregular network (50,2% *vs* 20% in non-SSM tumours, p < 0.001), irregular globuli (36.2% *vs* 16.4%, p = 0.008), irregular streaks (31% *vs* 7.3%, p < 0.001), shiny white streaks (24.1% *vs* 9.1%, p = 0.02), peppering (38.8% *vs* 18.2%, p = 0,007) and blue-white veil (42.2 *vs* 25.5%, p = 0.034). See figure 5 and 6 for examples of SSM.

Diameter, Breslow thickness and mitotic index were strongly depending on histologic subtype (see table 3). In turn, these three variables also influenced the dermoscopic findings. Diameter correlated positively with the number of colours and structures (p < 0.001). Colours white and blue-grey, ulceration, negative network, regular streaks and asymmetrically pigmented hair follicles correlated positively with diameter (p < 0.05). In turn, Breslow index correlated with number of colours (p < 0.001), but not with number of structures. Colour red, ulceration, irregular streaks, shiny white streaks, blue-white veil, milky-red areas and polymorphous vessels were more often in thicker lesions whereas dark and light brown, irregular network and peppering were more frequent in thinner melanomas (p < 0.05).

Prevalence of pigmentary traits and their influence on clinico-pathologic parameters

As a study carried out in a single institution, most patients were Mediterranean. Very few patients were skin type I, had red hair or green eyes. For this reason, patients were grouped together in “sensitive” skin type (phototype I and II) and “tan” (phototype III and IV). Similarly, red haired were put together with blond (red/blond hair) and brown haired together with black (dark hair).

A sensitive phototype - Fitzpatrick type I or II - was detected in 48 patients (28.1% of the sample) whereas a tan skin type - Fitzpatrick III and IV - was detected in the remaining 123 cases (71.9%). Clinical and histological data of both groups are summarized in table 4. Tan skinned patients were older at time of diagnosis compared to fair skin types (66.3 yo vs 59.8 yo respectively; p = 0.017) and had a significant higher incidence of LMM (29.3% *vs* 8.3% respectively, p = 0.004). Given

that LMM is often diagnosed in older individuals we compared differences in age at presentation excluding LMM. Tan-skin individuals were still older yet statistical significance was not reached (62,9 *vs* 59 years old, p = 0.183). As LMM is most often seen on the face and the scalp, head and neck was much more often the localization in tan individuals (26% *vs* 6.2%, p = 0.004). Excluding LMM cases, only 7 melanomas were located on the head and neck region, all in the tan group: one NM and six SSM.

Impact of pigmentary traits on dermoscopic findings

The prevalence of dermoscopic colours and structures in both sensitive and tan skinned individuals is shown in table 5. Colours showed some differences between tan and sensitive-skinned patients. Dark brown was more often seen in tan (93.5% vs 79.2% p = 0.006) and red in sensitive-skinned patients, although the difference did not reach significance (32.5% in tan vs 47.9% in sensitive skinned, p = 0.077). In regards to structures, milky-red areas were found in 33.3% of sensitive-skinned individuals *vs* 14.6% of tan-skinned patients (p = 0.006). Dermoscopic signs of LMM (pseudonetwork, assymetric pigmentated follicles and annular-granular structures) were tightly related to tan-skinned individuals. This was expected as LMM was much more common in the tan group. The prevalence of other dermoscopic colours and structures assessed did not show significant differences between tan and sensitive patients. Finally, the number of colours (3.8 in tan *vs* 3.9 on average in sensitive) and structures (3.8 in both groups on average) was almost identical between phototypes.

SSM was the only subtype of melanoma with a sufficient number of cases (n = 116, 79 in tan, 37 in sensitive-skinned individuals) to see the effect of phototype on the configuration of the tumour independently of the histological variant. LMM was the second group, but almost all lesions were in tan skinned patients (36/40, 90%), and the other two subtypes were far two small to make any subanalysis.

Taking only SSM, lesion diameter, Breslow and mitotic indexes and localization did not differ between phototypes. The colour red was more often seen in sensitive

patients (48.6% *vs* 29.1% p = 0.04) and so did also colour light brown (91.9% of sensitive patients *vs* 74.7 of tan, p = 0.03). In contrast, dark brown showed a tendency towards tan skinned individuals, although the difference was not statistically significant (97.5% of tan *vs* 89.2% of sensitive individuals showing dark brown on their lesions, p = 0.061). Milky-red areas were also more frequently observed in SSM in sensitive-skinned individuals (35.1% *vs* 17.7% p = 0.039). The other colours and structures, and the number of colours and structures present in the lesions, did no differ between skin types.

Multivariate analysis

In order to control possible confounding variables, we built a regression model for multivariate analysis introducing histologic subtype, lesion diameter, Breslow and Mitotic index as possible predictors combined with phototype, hair colour and eyes colour. The outcome variables were colours dark brown and red and milky-red areas (see table 6 for confidence intervals, IC 95%).

In our models, dark brown was positively related to a tan skin phototype, with an odds ratio (OR) for sensitive skin of 0.226. That is, tan individuals had an OR for having dark brown in their lesions of 4.434. However, dark brown was not related to hair and eyes colour, as OR were not significant. Red was conversely more often seen in sensitive-skinned patients with an OR of 2.412 and in patients with blue/green eyes with an OR 2.844. Hair colour was again not significant for red in dermoscopy. Finally, a sensitive-skin type, red/blond hair and blue/green eyes were all positive predictors for the presence of milky-red areas with an OR of 2.962, 3.503 and 3.091, respectively.

Discussion

Skin colour seems to be the result of complex molecular processes. The major determinant of human pigmentation is the Melanocortin 1 Receptor (*MC1R*) gene. Upon activation, MC1R stimulates cAMP production inducing a switch of pigment production from pheomelanin to eumelanin. Certain mutations in the *MC1R* gene, the so-called RHC polymorphisms, increase the expression of phaeomelanin in melanocytes, which is less sun protective and is responsible for red hair colour.[21] Other *MC1R* polymorphisms also determine the sun sensitivity in individuals without red hair.[22] In addition, evidence implicates this gene in skin carcinogenesis as polymorphisms related to the RHC phenotype and also not linked to pigmentation changes have been found to correlate with increased melanoma risk.[23-27] A very recent multicentric European study suggests that this effect may be in fact more important in darker pigmented Caucasians.[28]

In turn, keratinocytes and fibroblasts have also been found to modulate melanogenesis along with inflammation, antioxidant mechanisms and DNA repair following UV exposure.[29-31] This could explain why skin with vitiligo in darker phototypes preserves the anti-oxidant capacity despite the loss of melanin.[32] This "biochemical fingerprint of phototype" is responsible for the differences in response to UV light in different individuals and is also probably implicated in the carcinogenesis of skin tumours too. [33]

This study we present here shows some relevant methodological differences compared to the previous publications on phototype and dermoscopy in melanoma. [17-19] First, we did not investigate *MC1R* mutations in our patients. We believe this is important in most clinical settings where the decision on whether to excise a lesion or not is based on anamnesis and physical examination. Generally, we do not know *MC1R* status in our patients. Moreover, as we already mentioned, the pigmentary phenotype is the result of multiple genetic and cellular mechanisms that are yet not completely understood. Second, we did not use any diagnostic algorithm in order to find differences between skin types. Melanomas are generally detected on an unconscious reference to the overall pattern

compared with the other nevi on the individual (the ugly duckling sign) rather than on an analytic process applied to an isolated lesion.[34-36] As skin type, age, and other individual circumstances influence the distribution and appearance of pigmented lesions, the decision on whether to excise a mole or not is often taken based on the patient's history and whole physical examination.[36]

However, we admit some limitations. First, the ascription of a phototype to an individual is a rather subjective method. This is not the case when patients are separated in groups depending on objective parameters like the presence of genetic mutations. Second, from the more than 600 patients with melanoma visited at the HGUV in 5 years, less than one third were available for this study. The lack of a good clinical picture (in part due to the fact that many patients where diagnosed outside the hospital) was an important handicap. The sample was not very large and quite homogeneous: very few patients had red hair and a phototype I or IV according to Fitzpatrick's classification. For this reason we grouped skin type I with II, III with IV and red haired with blonds.

We found very few studies dealing with the prevalence of the different phototypes across the populations. In Spain, a Mediterranean country with mostly Caucasians and very few black or Asian individuals, only one study dealing with phototherapy and solar simulation indirectly evaluated the prevalence of the Fitzpatrick's phototypes.[37] They concluded that the most prevalent skin types seen in Spanish dermatologic clinics were II and III. It is generally considered that fairer, more sensitive skin types are more prevalent in northern countries in Europe. If that was the case, a multicentric, international study comprising more heterogeneous populations from different countries could yield more conclusive results.

What appears to be more established is that melanoma is relatively rare in Spain compared to other European countries. A very recent review came out with an incidence of 8.76 new cases/100 000 person-years,[38] lower than in Italy where 12.5 melanomas are diagnosed per 100 000 males and 13.1 per 100 000 females.[39] Greece is the country with the lowest incidence of melanoma in Europe (3 to 5 cases per 100 000 person years).[40] In contrast, northern European countries report

an incidence of 19 cases per 100 000 inhabitants.[41] The incidence in northern African countries, limiting with Spain to the south, falls to 0.14-0.4 new cases per 100 000 inhabitants.[42] That these differences in the incidence are related to the grade of sun sensitivity among the population of these countries is largely assumed in the literature. However environmental factors such as patterns of sun exposure, or inherited, genetic risk factors with variable prevalence may well play an important role.

Aside from the cancer registries, the Spanish National Cutaneous Melanoma Registry (RNMC) is a multicentric, on-line database that contains to date more than 17 000 cases registered and updated by their dermatologists. The aim of this project is to record the characteristics of melanoma at diagnosis. In a paper published by the group in 2013,[44] they described 13 628 melanomas diagnosed between 1997 and 2011. Unfortunately they did not mention phototype or pigmentary traits. In their series, a 56.5% of the patients were women and 43.5% were men. The mean age of the group was 57 years. The most common tumor site was the trunk, followed by the lower limbs. The most frequent pathologic subtype was SSM (62.6%), followed by NM (16.8%). Men were diagnosed 2.2 years older than women on average.

Our sample, in contrast, contains more men than women (99 and 72 respectively). In accordance with the RNMC and other published literature,[44,45] women presented more often with lesions located on the limbs, especially the lower limbs (22.2% vs 8.1% in males, p = 0.009), whereas men exhibited a higher proportion of melanomas on the head and neck region (26.3% *vs* 12.5% in females, p = 0.028). Males, compared to females, tended to present with larger (14.02 mm *vs* 12.68 mm respectively) and deeper lesions (1.009 mm *vs* 0.892 mm respectively), although differences were not statistically significant.

SSM was the most frequent histological subtype (n = 116), followed by LMM (n= 40). NM and ALM were rare (n = 7 and n = 8, respectively). This was surprising as it differs from international and Spanish cancer registries, including the RNMC, where NM comes after SSM in incidence rates.[44,47] A possible explanation is that we included both lentigo maligna (i.e. *in situ* melanoma) together with lentigo maligna

melanoma (invasive). However, taking into account only invasive lesions (n = 126), LMM was still the second subtype with 17 cases. Of course this can be biased, as the numbers are small.

Lesion diameter, Breslow index and mitotic index differed considerably between histological subtypes. The high average Breslow index and diameter, along with the significant correlation with ulceration dermoscopically visible in ALM is consistent with the fact that this histologic subtype is diagnosed late as an advanced tumour and carries a worse prognosis compared to other variants (see figure 3).[48,49]

As expected, dermoscopic findings correlated with the morphological characteristics - diameter, Breslow index, mitotic index and histologic subtype - of the melanomas. LMM and ALM showed their well-known dermoscopic criteria attributed to their specific anatomic location.[50-52] Ulceration and milky-red areas were often seen in NM, as already described in the literature.[53] Globuli, streaks and network, along with colour dark brown and black, which correlate histologically to the presence of melanocytes at the dermo-epidermal junction or the papillary dermis[54] were most often seen in SSM. The fact that light brown was more often detected in LMM and dark brown in SSM in our sample rely upon their histological characteristics. LMM displays sometimes a subtle increase in the number of melanocytes only, which generally remain attached to the junction, whereas in SSM pagetoid spread is conspicuous resulting in much higher loads of melanocytes and consequently melanin on the epidermis (see figure 4).[55]

Skin type did not influence significantly the location, diameter or Breslow index in our patients. The age at presentation was slightly higher in tan patients. We found a positive correlation between LMM and a tan skin phototype that was not previously described in the literature. In line with this, a MC1R polymorphism not associated with the RHC phenotype was linked to LMM in a Mediterranean population.[27] In turn, despite the small numbers, NM was more often diagnosed in sensitive skinned individuals than in tan (8,3 *vs* 2,4% respectively). The tendency towards a higher proportion of NM presenting in lighter skin types was already

mentioned by Farignoli et al.[19] Further epidemiological studies should revaluate these tendencies, but this could explain the lower incidence of NM in our sample.

Regarding the variation in dermoscopic findings depending on skin type, we did not find differences in the number of colours and structures depending on the phototype. The same result was obtained when histologic subtypes including only SSM in the analysis. This contrasts with the previous studies that used the ABCD algorithm of dermoscopy and found a higher total dermoscopy score in tan patients.[17,19] The colour dark brown was more often seen in tan individuals than in sensitive (93.5% *vs* 79.2% respectively). Conversely, milky-red areas were more often exhibited by melanomas on sensitive skin compared to tan (33.3% *vs* 14.6% respectively). Taking only SSM, the numbers were similar. In this subanalysis, a significantly higher percentage of the lesions in sensitive contained the colour light brown (91.9% in sensitive *vs* 74.7% in tan). These findings indicate that melanomas in tan individuals may keep the capacity to produce more melanin than tumours in lighter skin types, just like their benign melanocytic nevi and the surrounding healthy skin.

Because the presence of dermoscopic structures was depending on histologic subtype, lesion diameter, Breslow and mitotic index, we tried to assess whether pigmentary traits and sun-sensitivity had still any influence when we controlled all these variables. In the multivariate analysis, the presence of the colour red and milky-red areas was predicted by a sensitive phototype with an OR of 2.412 and 2.962 respectively. Tan individuals had an OR for the presence of colour dark brown of 4.434. Other pigmentary traits also correlated with these findings. Red/blond hair predicted the presence of milky-red areas with an OR of 3.503 compared to dark hair and green/blue eyes colour correlated in dermoscopy with the presence of colour red (OR = 2.844) and milky-red areas (OR = 3.091).

In conclusion, our study correlates the pigmentary traits evaluated clinically with the dermoscopical and some histological traits in melanomas. Tan skinned individuals were slightly older at presentation and presented more often with LMM. Lesion diameter and Breslow index were similar in both tan and sensitive-

skin types. In sensitive skin, melanomas exhibited more often red colour and milky-red areas. Colour dark brown was associated with a tan skin type. This could reflect that melanomas in darker skin types probably keep the capacity to produce high amounts of eumelanin that makes them look darker. The knowledge of these differences may aid the clinician in the correct approach to the melanocytic lesions in a given individual. Future studies with larger numbers should investigate the incidence of the different histologic subgroups of melanoma among the skin types in Caucasians as this may be relevant in the design of specific preventive and screening strategies.

References

1. Gandini S, Sera F, Cattaruzza MS, Pasquini P , Zanetti R, Masini C, et al. Metanalysis of risk factors for cutaneous melanoma: iii. Family history, actinic damage and phenotypic factors. Eur J Cancer . 2005;41:2040-59.
2. Elwood JM, Whitehead SM, Davison J, Stewart M, Galt M. Malignant melanoma in England: risks associated with naevi, freckles, social class, hair colour , and sunburn. Int J Epidemiol. 1990;19:801-10.
3. Rodenas JM, Delgado-Rodriguez M, Herranz MT, Tercedor J, Serrano S. Sun exposure, pigmentary traits, and risk of cutaneous malignant melanoma: a case-control study in a Mediterranean population. Cancer Causes Control. 1996;7:275-83.
4. Beitner H, Norell SE, Ringborg U, Wennersten G, Mattson B. Malignant melanoma: aetiological importance of individual pigmentation and sun exposure. Br J Dermatol. 1990;122: 43-51.
5. Holman CD, Armstrong BK. Pigmentary traits, ethnic origin, benign nevi, and family history as risk factors for cutaneous malignant melanoma. J Natl Cancer Inst. 1984;72:257-66.
6. Bliss JM, Ford D, Swerdlow AJ, Armstrong BK, Cristofolini M, Elwood JM, Green A, Holly EA, Mack T, MacKie RM, et al. Risk of cutaneous melanoma associated with pigmentation characteristics and freckling: systematic overview of 10 case-control studies. The International Melanoma Analysis Group (IMAGE). Int J Cancer. 1995;62:367-76.
7. Grulich AE, Bataille V, Swerdlow AJ, Newton-Bishop JA, Cuzick J, Hersey P, McCarthy WH. Naevi and pigmentary characteristics as risk factors for melanoma in a high-risk population: a case-control study in New South Wales. Australia. Int J Cancer. 1996;67:485-91.
8. Bakos L, Wagner M, Bakos RM, Leite CS, Sperhacke CL, Dzekaniak KS, Gleisner AL. Sunburn, sunscreens, and phenotypes: some risk factors for cutaneous melanoma in southern Brazil. Int J Dermatol. 2002 Sep;41:557-62.
9. Chiarugi A, Ceroti M, Palli D, Cevenini G, Guarrera M, Carli P. Sensitivity to ultraviolet B is a risk factor for cutaneous melanoma in a Mediterranean

population: results from an Italian case-control study. Clin Exp Dermatol. 2009;34:8-15.

10. Zalaudek I, Argenziano G, Mordente I, Moscarella E, Corona R, Sera F, Blum A, Cabo H, Di Stefani A, Hofmann-Wellenhof R, Johr R, Langford D, Malvehy J, Kolm I, Sgambato A, Puig S, Soyer HP, Kerl H. Nevus type in dermoscopy is related to skin type in white persons. Arch Dermatol. 2007;143:351-356.
11. Lallas A, Reggiani C, Argenziano G, Kyrgidis A, Bakos R, Masiero NC, Scheibe AB, Cabo H, Ozdemir F, Sortino-Rachou AM, Turk BG, Moscarella E, Longo C, Zalaudek I. Dermoscopic nevus patterns in skin of colour: a prospective, cross-sectional, morphological study in individuals with skin type V and VI. J Eur Acad Dermatol Venereol. 2014 Nov;28:1469-74.
12. Tuma B, Yamada S, Atallah ÁN, Araujo FM, Hirata SH. Dermoscopy of black skin: A cross-sectional study of clinical and dermoscopic features of melanocytic lesions in individuals with type V/VI skin compared to those with type I/II skin. J Am Acad Dermatol. 2015;73:114-9.
13. Bakos RM, Argenziano G, Zalaudek I, Masiero NC, Zoratto G, Cartell A, Bakos L. Dermatoscopy of pigmented melanocytic nevi in patients with oculocutaneous albinism. J Am Acad Dermatol. 2009;60:487-9.
14. De Luca DA, Bollea Garlatti LA, Galimberti GN, Galimberti RL. Amelanotic melanoma in albinism: the power of dermatoscopy. J Eur Acad Dermatol Venereol. 2015 IN PRESS.
15. Zalaudek I, Hofmann-Wellenhof R, Cerroni L, Kerl H. White dysplastic melanocytic naevi. Lancet. 2002;359:1999-2000.
16. Zalaudek I, Meiklejohn W, Argenziano G, Thurber AE, Sturm RA. "White" nevi and "red" melanomas: association with the RHC phenotype of the MC1R gene. J Invest Dermatol. 2009;129:1305-7.
17. Cuéllar F, Puig S, Kolm I, Puig-Butille J, Zaballos P, Martí-Laborda R, Badenas C, Malvehy J. Dermoscopic features of melanomas associated with MC1R variants in Spanish CDKN2A mutation carriers. Br J Dermatol. 2009;160:48-53.
18. Quint KD, van der Rhee JI, Gruis NA, Ter Huurne JA, Wolterbeek R, van der Stoep N, Bergman W, Kukutsch NA. Melanocortin 1 receptor (MC1R)

variants in high melanoma risk patients are associated with specific dermoscopic ABCD features. Acta Derm Venereol. 2012;92:587-92.

19. Fargnoli MC, Sera F, Suppa M, Piccolo D, Landi MT, Chiarugi A, Pellegrini C, Seidenari S, Peris K. Dermoscopic features of cutaneous melanoma are associated with clinical characteristics of patients and tumours and with MC1R genotype. J Eur Acad Dermatol Venereol. 2014;28:1768-75.
20. Argenziano G, Soyer HP, Chimenti S, Talamini R, Corona R, Sera F, Binder M, Cerroni L, De Rosa G, Ferrara G, Hofmann-Wellenhof R, Landthaler M, Menzies SW, Pehamberger H, Piccolo D, Rabinovitz HS, Schiffner R, Staibano S, Stolz W, Bartenjev I, Blum A, Braun R, Cabo H, Carli P, De Giorgi V, Fleming MG, Grichnik JM, Grin CM, Halpern AC, Johr R, Katz B, Kenet RO, Kittler H, Kreusch J, Malvehy J, Mazzocchetti G, Oliviero M, Ozdemir F, Peris K, Perotti R, Perusquia A, Pizzichetta MA, Puig S, Rao B, Rubegni P, Saida T, Scalvenzi M, Seidenari S, Stanganelli I, Tanaka M, Westerhoff K, Wolf IH, Braun-Falco O, Kerl H, Nishikawa T, Wolff K, Kopf AW. Dermoscopy of pigmented skin lesions: results of a consensus meeting via the Internet. J Am Acad Dermatol. 2003;48:679-93.
21. Flanagan N, Healy E, Ray A Philips S, Todd C, Jackson IJ, Birch-Machin MA, Rees JL. Pleiotropic effects of the melanocortin 1 receptor (MC1R) gene on human pigmentation. Hum Mol Genet 2000; 9:2531–7.
22. Healy E, Flannagan N, Ray A, Todd C, Jackson IJ, Matthews JN, Birch-Machin MA, Rees JL. Melanocortin-1-receptor gene and sun sensitivity in individuals without red hair. Lancet. 2000;355:1072–3.
23. Chatzinasiou F, Lill CM, Kypreou K, Stefanaki I, Nicolaou V, Spyrou G, Evangelou E, Roehr JT, Kodela E, Katsambas A, Tsao H, Ioannidis JP, Bertram L, Stratigos AJ. Comprehensive field synopsis and systematic meta-analyses of genetic association studies in cutaneous melanoma. J Natl Cancer Inst 2011;103:1227– 35.
24. Kennedy C, ter Huurne J, Berkhout M, Gruis N, Bastiaens M, Bergman W, Willemze R, Bavinck JN. Melanocortin 1 receptor (MC1R) gene variants are associated with an increased risk for cutaneous melanoma which is largely independent of skin type and hair color. J Invest Dermatol 2001; 117:294–300.

25. Duffy DL, Box NF, Chen W, Palmer JS, Montgomery GW, James MR, Hayward NK, Martin NG, Sturm RA. Interactive effects of MC1R and OCA2 on melanoma risk phenotypes. Hum Mol Genet 2004; 13:447– 61.
26. Williams PF, Olsen CM, Hayward NK, Whiteman DC. Melanocortin 1 receptor and risk of cutaneous melanoma: a meta-analysis and estimates of population burden. Int J Cancer 2011;129:1730– 40.
27. Puig-Butillé JA, Carrera C, Kumar R, Garcia-Casado Z, Badenas C, Aguilera P, Malvehy J, Nagore E, Puig S. Distribution of MC1R variants among melanoma subtypes: p.R163Q is associated with lentigo maligna melanoma in a Mediterranean population. Br J Dermatol. 2013;169:804-11.
28. Pasquali E, García-Borrón JC, Fargnoli MC, Gandini S, Maisonneuve P, Bagnardi V, Specchia C, Liu F, Kayser M, Nijsten T, Nagore E, Kumar R, Hansson J, Kanetsky PA, Ghiorzo P, Debniak T, Branicki W, Gruis NA, Han J, Dwyer T, Blizzard L, Landi MT, Palmieri G, Ribas G, Stratigos A, Council ML, Autier P, Little J, Newton-Bishop J, Sera F, Raimondi S; M-SKIP Study Group. MC1R variants increased the risk of sporadic cutaneous melanoma in darker-pigmented Caucasians: a pooled-analysis from the M-SKIP project. Int J Cancer. 2015;136:618-31.
29. Cario-André M, Pain C, Gauthier Y, Casoli V, Taieb A. In vivo and in vitro evidence of dermal fibroblasts influence on human epidermal pigmentation. Pigment Cell Res. 2006;19:434-42.
30. Kovacs D, Flori E, Maresca V, Ottaviani M, Aspite N, Dell'Anna ML, Panzella L, Napolitano A, Picardo M, d'Ischia M. The eumelanin intermediate 5,6-dihydroxyindole-2-carboxylic acid is a messenger in the cross-talk among epidermal cells. J Invest Dermatol. 2012;132:1196-205.
31. Bessou-Touya S, Picardo M, Maresca V, Surlève-Bazeille JE, Pain C, Taïeb A. Chimeric human epidermal reconstructs to study the role of melanocytes and keratinocytes in pigmentation and photoprotection. J Invest Dermatol. 1998;111:1103-8.
32. Briganti S, Caron-Schreinemachers AL, Picardo M, Westerhof W. Anti-oxidant defence mechanism in vitiliginous skin increases with skin type. J Eur Acad Dermatol Venereol 2012;26:1212–1219.

33. Maresca V, Flori E, Picardo M. Skin phototype: a new perspective. Pigment Cell Melanoma Res. 2015;28:378-89.
34. Gachon J, Beaulieu P, Sei JF, Gouvernet J, Claudel JP, Lemaitre M, Richard MA, Grob JJ. First prospective study of the recognition process of melanoma in dermatological practice. Arch Dermatol. 2005;141 (4):434-438.
35. Scope A, Dusza SW, Halpern AC, et al. The “ugly duckling” sign: agreement between observers. Arch Dermatol. 2008;144(1):58-64.
36. Zalaudek I, Docimo G, Argenziano G. Using dermoscopic criteria and patient-related factors for the management of pigmented melanocytic nevi.Arch Dermatol. 2009;145:816-26.
37. Pérez Ferriols A, Aguilera J, Aguilera P, de Argila D, Barnadas MA, de Cabo X, Carrrascosa JM, de Gálvez Aranda MV, Gardeazábal J, Giménez-Arnau A, Lecha M, Lorente J, Martínez-Lozano JA, Rodríguez Granados MT, Sola Y, Utrillas MP; del Grupo Español de Fotobiología. Determinación de la dosis eritemática mínima y reacciones anómalas a radiación ultravioleta A según fototipo. Actas Dermosifiliogr. 2014;105:780-8.
38. Tejera-Vaquerizo A, Descalzo-Gallego MA, Otero-Rivas MM, Posada-García C, Rodríguez-Pazos L, Pastushenko I, Marcos-Gragera R, García-Doval I. Incidencia y mortalidad del cáncer cutáneo en España: revisión sistemática y metaanálisis. Actas Dermosifiliogr. 2016 IN PRESS
39. AIRT Working Group Italian cancer figures-report 2006: 1. Incidence, mortality and estimates. Epidemiol. Prev. 2006;30:8–10.
40. Talaganis JA, Biello K, Plaka M, Polydorou D, Papadopoulos O, Trakatelli M, Sotiriadis D, Tsoutsos D, Kechagias G, Gogas H, Antoniou C, Swetter SM, Geller AC, Stratigos AJ. Demographic, behavioural and physician-related determinants of early melanoma detection in a low-incidence population. Br J Dermatol. 2014;171:832-8.
41. Nikolaou V, Stratigos AJ. Emerging trends in the epidemiology of melanoma. Br J Dermatol. 2014;170:11-9.
42. El Euch D, Zaraa I, Driss M, Fourati M, Mokni M, Rahal K, Ben Rodhane K, Ben Osman A. Le mélanome en Tunisie : etude anatomoclinique de 46 cas. Ann Dermatol Venereol. 2010;137:391-2.
43. www.registromelanoma.es

44. Ríos L, Nagore E, López JL, Redondo P, Martí RM, Fernández-de-Misa R, Soler B. Melanoma characteristics at diagnosis from the Spanish National Cutaneous Melanoma Registry: 15 years of experience. Actas Dermosifiliogr. 2013;104:789-99.
45. Blois MS, Sagebiel RW, Abarbanel RM, Caldwell TM, Tuttle MS. Malignant melanoma of the skin. I. The association of tumor depth and type, and patient sex, age, and site with survival. Cancer, 1983;52:1330-1341.
46. Vossaert KA, Silverman MK, Kopf AW, Bart RS, Rigel DS, Friedman RJ, Levenstein M. Influence of gender on survival in patients with stage 1 malignant melanoma. J Am Acad Dermatol, 1992;26:429-440.
47. Katalinic A, Kunze U, Schäfer T. Epidemiology of cutaneous melanoma and non-melanoma skin cancer in Schleswig-Holstein, Germany: incidence, clinical subtypes, tumour stages and localization (epidemiology of skin cancer). Br J Dermatol. 2003;149:1200-6.
48. Bradford PT, Goldstein AM, McMaster ML, Tucker MA. Acral lentiginous melanoma: incidence and survival patterns in the United States, 1986-2005. Arch Dermatol. 2009;145:427-34.
49. Shaikh WR, Dusza SW, Weinstock MA, Oliveria SA, Geller AC, Halpern AC. Melanoma Thickness and Survival Trends in the United States, 1989 to 2009. J Natl Cancer Inst. 2015;108(1).
50. Stolz W, Schiffner R, Burgdorf WH. Dermatoscopy for facial pigmented skin lesions. Clin Dermatol. 2002;20:276-8.
51. Pralong P, Bathelier E, Dalle S, Poulalhon N, Debarbieux S, Thomas L. Dermoscopy of lentigo maligna melanoma: report of 125 cases. Br J Dermatol. 2012;167:280-7.
52. Saida T, Oguchi S, Miyazaki A. Dermoscopy for acral pigmented skin lesions. Clin Dermatol. 2002;20:279-85.
53. Menzies SW, Moloney FJ, Byth K, Avramidis M, Argenziano G, Zalaudek I, Braun RP, Malvehy J, Puig S, Rabinovitz HS, Oliviero M, Cabo H, Bono R, Pizzichetta MA, Claeson M, Gaffney DC, Soyer HP, Stanganelli I, Scolyer RA, Guitera P, Kelly J, McCurdy O, Llambrich A, Marghoob AA, Zaballos P, Kirchesch HM, Piccolo D, Bowling J, Thomas L, Terstappen K, Tanaka M, Pellacani G, Pagnanelli G, Ghigliotti G, Ortega BC, Crafter G, Ortiz AM,

Tromme I, Karaarslan IK, Ozdemir F, Tam A, Landi C, Norton P, Kaçar N, Rudnicka L, Slowinska M, Simionescu O, Di Stefani A, Coates E, Kreusch J. Dermoscopic evaluation of nodular melanoma. JAMA Dermatol. 2013;149:699-709.

54. Stante M, De Giorgi V, Cappugi P, Giannotti B, Carli P. Non-invasive analysis of melanoma thickness by means of dermoscopy: a retrospective study. Melanoma Res. 2001;11:147-52.
55. Clark WH, Mihm MC. Lentigo maligna and lentigo-maligna melanoma. Am J Pathol. 1969; 55: 39–67.

Appendix

Tables

TABLE 1

Colours	White
	Red
	Light brown
	Dark Brown
	Black
	Blue-grey
Network	Regular
	Irregular
	Negative
Globules	Regular
	Irregular
	Peripheral
Streaks	Regular
	Irregular
	Shiny white streaks (chrysalis)
Blotches/dots	Regular
	Irregular
Vessels	Comma
	Dotted
	Polymorphous
Regression	"Peppering"
	Scar-like
Other Features	Ulceration
	Milky-red areas
	Blue-white veil
ALM-associated features	Parallel-ridge pattern
	Parallel-furrow pattern
	Fibrillar pattern
	Lattice-like pattern
LM-associated features	Pseudonetwork
	Assymetric pigmentated follicles
	Annular-granular structures

Table 1. Colours and structures analysed in dermoscopic images. LM: lentigo maligna. ALM: acral lentiginous melanoma. Within LM-associated features, obliteration of hair follicles was included as "blotches"

TABLE 2

		Men	Women	All
Number		99 (57.9)	72 (42.1)	171 (100)
Age		65,1	63,5	64,4
Histologic Subtype (%)	SSM	70 (70.7)	46 (63.9)	116 (67.8)
	LMM	25 (25.3)	15 (20.9)	40 (23.4)
	ALM	3 (3)	5 (6.9)	8 (4.7)
	NM	1 (1)	6 (8.3)	7 (4.1)
Location (%)	Head & neck	26 (26.3)	9 (12.5)	35 (20.5)
	Trunk	45 (45.5)	24 (33.3)	69 (40.4)
	Upper limb	17 (17.2)	18 (25)	35 (20.5)
	Lower limb	8 (8.1)	16 (22.2)	24 (14.0)
	Hands & feet	3 (3)	5 (6.9)	8 (4.7)
Diameter (mm)		14.02	12.681	13.456
Breslow index (mm)		1.009	0.892	0.96
Mitotic index (mit/cm^2)		2.342	2.094	2.238

Table 2. Average age, histologic subtypes, localization, size and Breslow and mitotic indexes for men and women. SSM was the most frequent histologic subtype and the trunk the most frequent location in both sexes. LMM was slightly more prevalent in men although the difference did not reach statistical significance. Women presented more often with lesions located on the limbs, especially the lower limbs (22.2% *vs* 8.1% in males, p = 0.009), whereas men exhibited a higher proportion of melanomas on the head and neck region (26.3% *vs* 12.5% in females, p = 0.028). Men tended to present with larger and deeper lesions exhibiting more mitosis, although differences are not statistically significant.

TABLE 3

	SMM	LMM	ALM	NM	
Number (%)	116 (67.8)	40 (23.4)	8 (4.7)	7 (4.1)	
Diameter (mm)	12.6	15.6	18	9.2	p = 0.011
Breslow (mm)	0.89	0.41	3.17	2.69	p < 0.001
Mitotic index (mit/cm^2)	1.9	1.35	5.5	6.29	p < 0.001

Table 3. Diameter, Breslow and mitotic index were tightly related to histologic subtype.

TABLE 4

		Tan	Sensitive	
n		123	48	
Sex (%)	Male	74 (60.2)	25 (52.1)	p = 0.336
	Female	49 (39.8)	23 (47.9)	
Age (y)		66.3	59.8	**p = 0.017**
Hair colour (%)	Dark	123 (100)	10 (20.8)	**p < 0.001**
	Red/blond	0 (0)	38 (79.2)	
Eyes colour (%)	Brown/black	103 (83.7)	6 (12.5)	**p < 0.001**
	Blue/green	20 (16.3)	42 (87.5)	
Localization (%)	Head and neck	32 (26.0)	3 (6.2)	p = 0.064
	Trunk	47 (38.2)	22 (45.9)	
	Upper limb	22 (17.9)	13 (27.1)	
	Lower limb	17 (13.8)	7 (14.6)	
	Acral skin	5 (4.1)	3 (6.2)	
Diameter (mm)		13.886	12.354	p = 0.207
Histology (%)	SSM	79 (64.2)	37 (77.1)	**p = 0.014**
	LMM	36 (29.3)	4 (8.3)	
	NM	3 (2.4)	4 (8.3)	
	ALM	5 (4.1)	3 (6.2)	
Breslow (mm)		0.95	0.96	p = 0.959
Mitotic index (mit/cm^2)		2.4	2.1	p = 0.707

Table 4. Clinical and histological data in tan and sensitive-skinned individuals. Statistically significant p-scores ($p < 0.05$) are highlighted in bold. Tan individuals were older at diagnosis and presented more frequently with LMM.

TABLE 5

		Tan (%)	Sensitive (%)	p
Colours	White	44 (35.8)	17 (35.4)	0.965
	Red	40 (32.5)	23 (47.9)	0.077
	Light brown	99 (80.5)	40 (83.3)	0.668
	Dark Brown	115 (93.5)	38 (79.2)	**0.006**
	Black	91 (74)	38 (79.2)	0.479
	Blue-grey	86 (70)	35 (72.9)	0.699
Average number of colours		3,862	3.979	0.985
Network	Regular	6 (4.9)	0 (0)	0.119
	Irregular	51 (41.5)	24 (50)	0.312
	Negative	4 (3.2)	3 (6.2)	0.374
Globuli	Regular	0 (0)	0 (0)	
	Irregular	35 (28.5)	16 (33.3)	0.531
	Peripheral	3 (2.4)	2 (4.2)	0.547
Streaks	Regular	3 (2.4)	0 (0)	0.275
	Irregular	28 (22.8)	12 (25)	0.756
	Chrysalis	23 (18.7)	10 (20.8)	0.751
Blotches/dots	Regular	3 (2.4)	0 (0)	0.275
	Irregular	58 (47.1)	24 (50)	0.738
Vessels	Comma	0 (0)	0 (0)	
	Dotted	6 (4.9)	4 (8.3)	0.387
	Polymorphous	15 (12.2)	10 (20.8)	0.151
Regression	“Peppering”	41 (33.3)	14 (29.2)	0.6
	Scar-like	35 (28.5)	10 (20.8)	0.309
Other Features	Ulceration	15 (12.2)	9 (18.7)	0.267
	Milky-red areas	18 (14.6)	16 (33.3)	**0.006**
	Blue-white veil	42 (34.1)	21 (43.7)	0.242
ALM features	Parallel-ridge	4 (3.2)	1 (2)	0.684
	Parallel-furrow	0 (0)	0 (0)	
	Fibrillar	1 (0.8)	0 (0)	0.531
	Lattice-like	1 (0.8)	0 (0)	0.531
LMM-associated features	Pseudonetwork	28 (22.8)	2 (4.2)	**0.004**
	Assymetric pigmentated follicles	27 (21.9)	3 (6.2)	**0.015**
	Annular-granular structures	24 (19.5)	3 (6.2)	**0.033**
Average number of structures		3,894	3.875	0.949

Table 5. Differences in dermoscopic findings between tan and sensitive-skinned individuals. Significant differences (in bold) were found in colour dark brown, which was more often seen in tan-skinned individuals and milky red areas, more often seen on sensitive skin. Red colour showed a tendency for sensitive skin, yet the difference did not reach statistical significance. Dermoscopic findings related to LMM were more often seen in tan, as LMM was much more frequent in tan-skinned individuals.

TABLE 6

	Sensitive phototype	Red/blond hair	Green/blue eyes
Dark brown	**0.226 (0.063-0.805)**	0.372 (0.106-1.31)	0.22 (0.108-1.194)
Red	**2.412 (1.089-5.342)**	2.108 (0.927-4.791)	**2.844 (1.341-6.031)**
Milky-red areas	**2.962 (1.206-7.72)**	**3.503 (1.392-8.817)**	**3.091 (1.282-7.452)**

Table 6. Dermoscopic signs found to be related to phototype in bivariate analysis were tested in multivariate analysis including histologic subtype, lesion diameter, Breslow and Mitotic index as possible predictors. Odds ratios (OR) and Confidence intervals of 95% (IC95%, shown in brackets) were calculated in a linear regression model. Significant odds ratios are highlighted in bold.

Figures

FIGURE 1

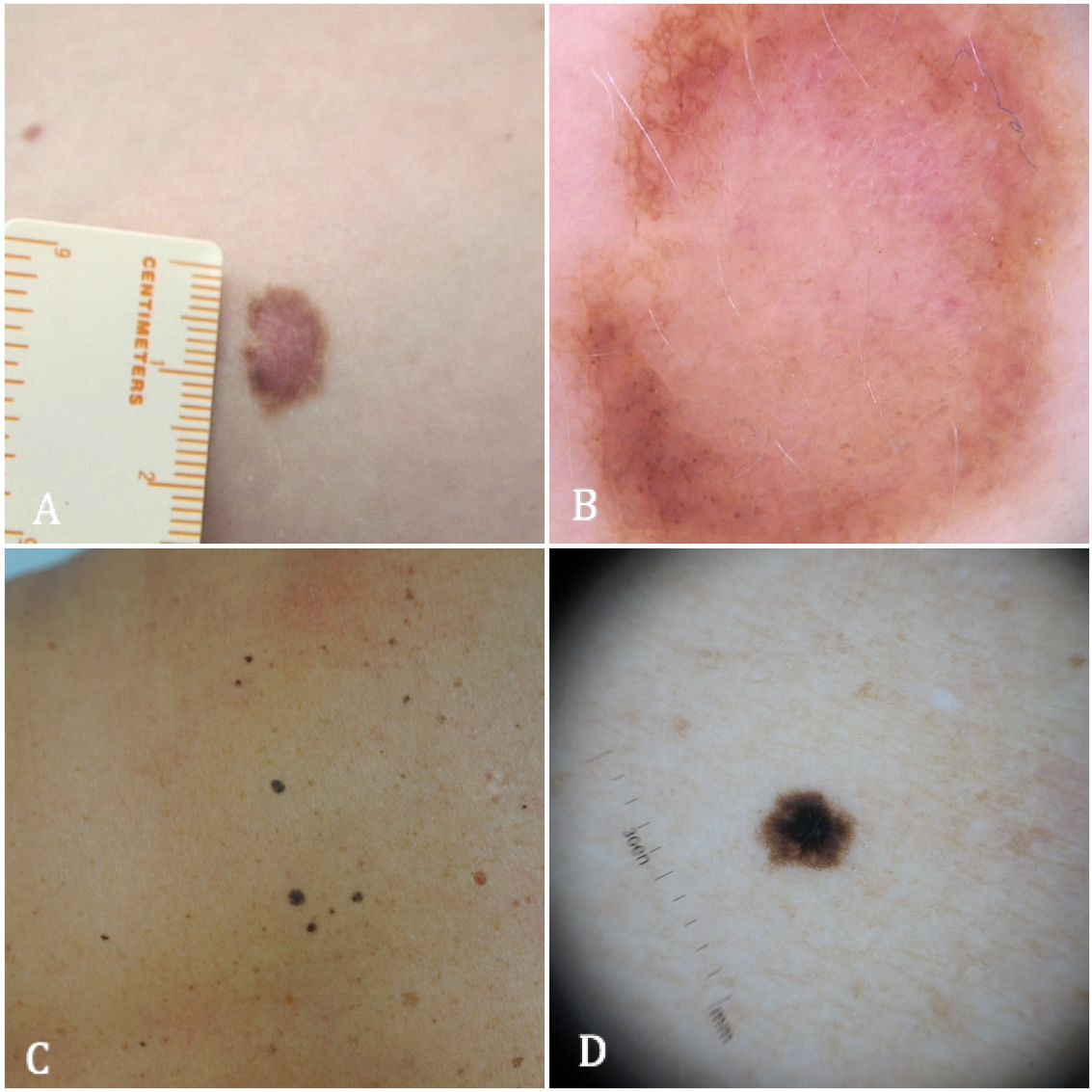

Figure 1: Fitzpatrick's skin type I (A and B) tend to develop large (> 5mm) nevi with light-brown coloration, reticular pattern, and central hypopigmentation, whereas patients with skin type IV (C and D) tend to show small (< 5mm) dark brown lesions with a central hyperpigmentation.

FIGURE 2

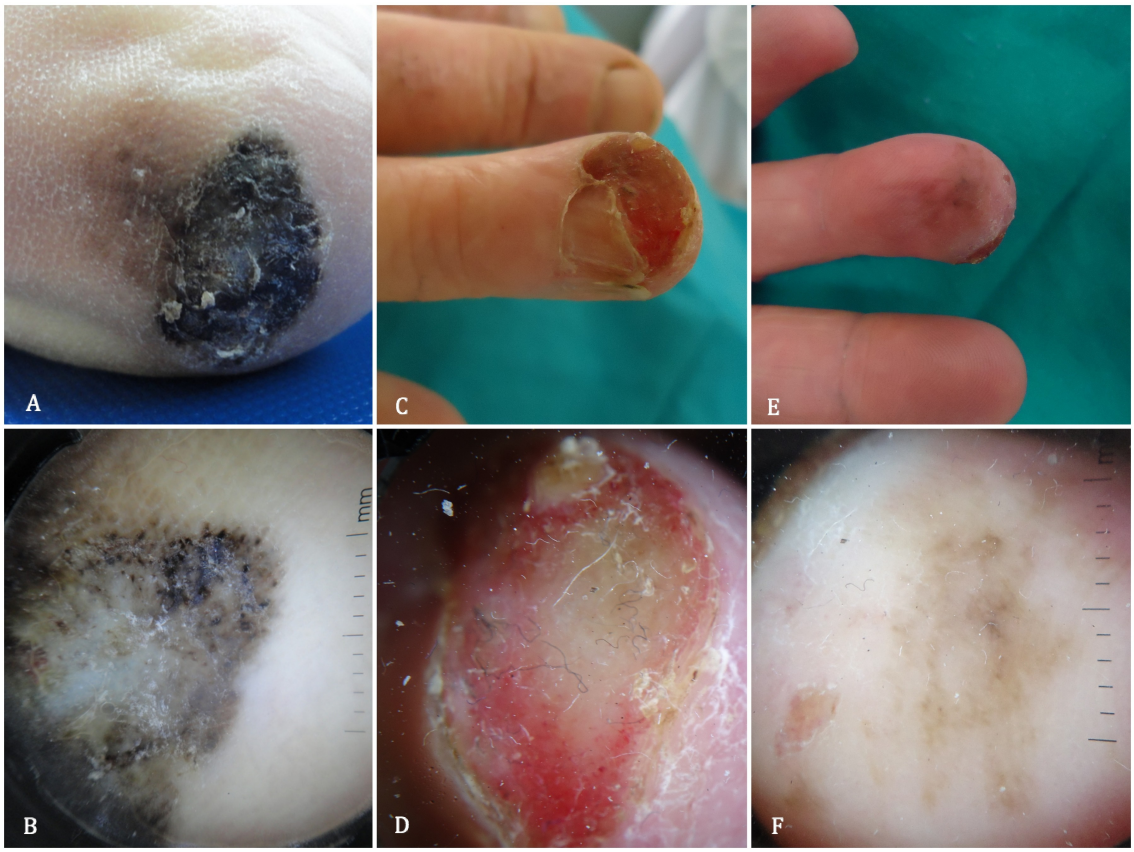

Figure 1: Examples of ALM in our sample. A and B correspond to patient #68 (male, 79 years old, sensitive skinned, ALM on the right heel, Breslow 1.8 mm). The lesion showed multiple signs of ALM (parallel ridge pattern, irregular globules, blue-white veil and ulceration). C, D, E and F correspond to patient #114 (female, 68 years old, tan skinned, ALM on the fourth finger of the right hand, Breslow 9.8 mm). Dermoscopically we could see a striking milky red area with polymorphous vessels and a surrounding parallel ridge pattern. See how in this patient the lesion affected the whole diameter of the finger, both palmar and dorsal surfaces. ALM showed more often ulceration than the other types (50% *vs* 12.3% respectively). In addition, it was the histological subtype with the highest diameters and Breslow indexes (18 mm and 3.17 mm on average, respectively). In contrast, mitotic index was higher in NM. All these numbers indicate how late are these tumours diagnosed.

FIGURE 3

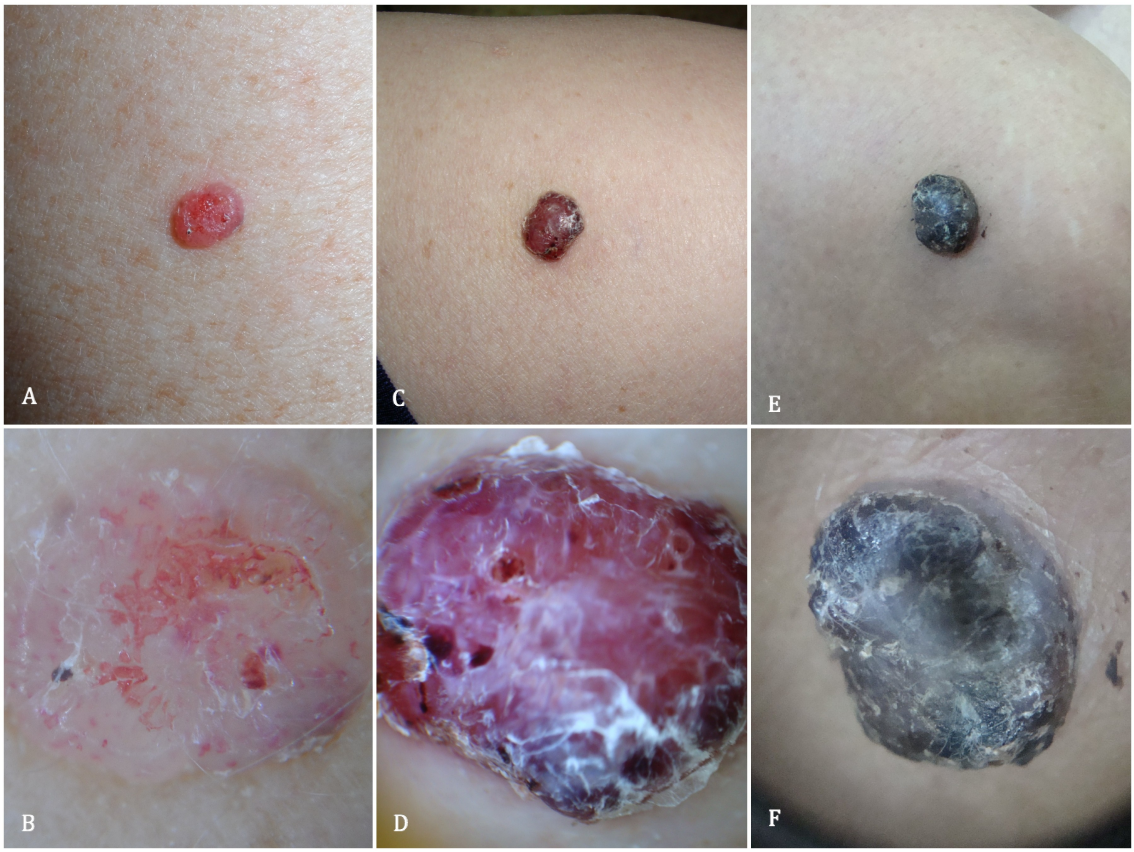

Figure 2: Examples of NM. A and B correspond to patient #110 (female, 57 years old, blond hair, blue/green eyes, sensitive skinned, NM on the right arm, Breslow 2 mm). See the milky red areas, polymorphous vessels and dermoscopic ulceration. C and D correspond to patient #113 (female, 71 years old, blond hair, blue/green eyes, sensitive skinned, NM on the left thigh, Breslow 4.2 mm). Dermoscopic signs identified are milky red areas, shiny-white streaks, blotches and polymorphous vessels. E and F correspond to patient #118 (female, 65 years old, dark hair, blue/green eyes, sensitive skinned, NM on the right knee, Breslow 3.8 mm). Dermoscopicaly we observed a blue-grey structureless area with shiny-white streaks and some darker dot. NM showed a clear tendency for sensitive-skinned individuals, although the numbers were small. Although ALM was the variant with the deepest Breslow index, NM showed the highest mitotic index (6.29 on average). This finding explains the rapid growth compared to other variants. NM correlated also with dermoscopic ulceration (42.9% *vs* 12.8% for other histologic subgroups), and milky-red areas (58.1% *vs* 18.3% for other melanoma subtypes).

FIGURE 4

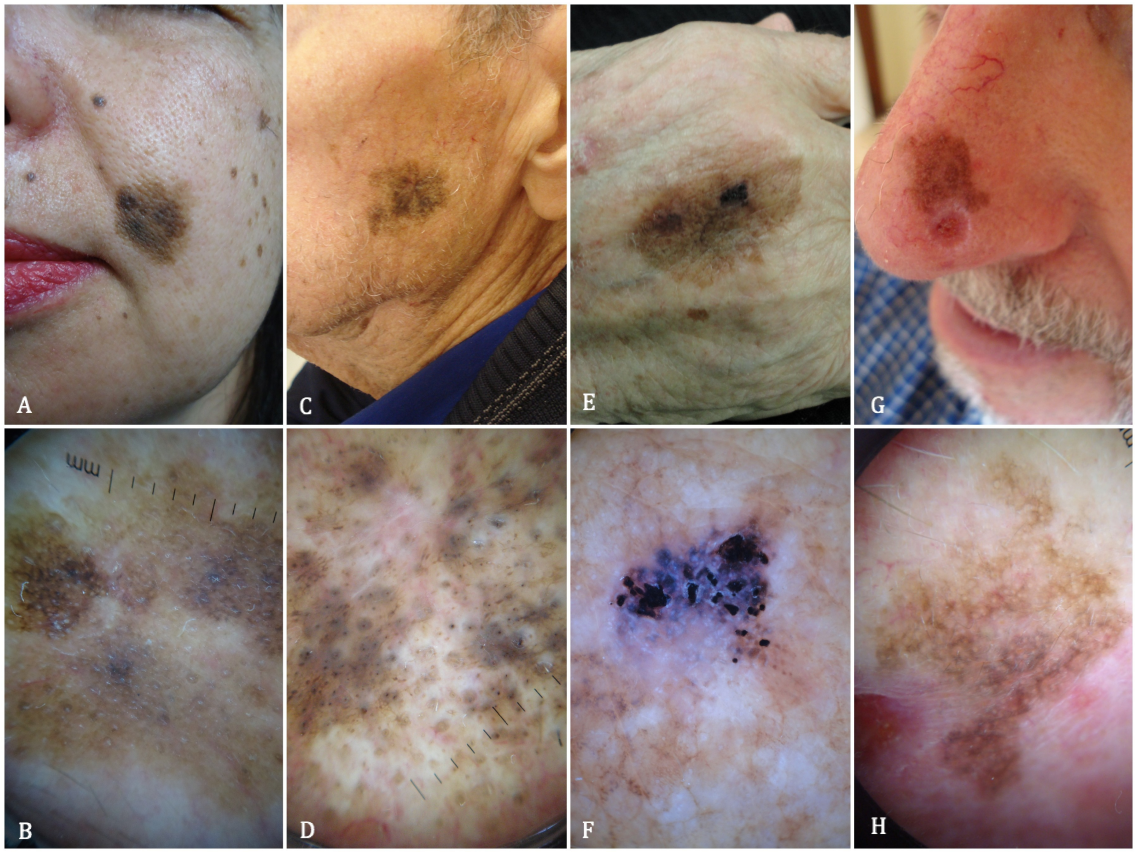

Figure 3: Examples of LMM. A and B: Patient #116 (female, 49 years old, tan skinned, LMM on the left cheek, Breslow 0.14 mm). See an atypical pseudonetwork with asymmetrically pigmented follicular ostia. C and D: Patient #125 (male, 73 years old, tan, LMM on the left cheek, Breslow 0.3 mm) exhibiting an atypical pseudonetwork, asymmetrically pigmented follicular ostia and blotches. E and F: Patient #123 (female, 88 yo, tan, LMM on the right hand, Breslow 0.38 mm). Dermoscopically anular granular structures, an atypical pseudonetwork and black blotches were observed. G and H: Patient #72 (male, 88 years old, tan, LMM on the nose, Breslow 0.12 mm). The lesion contained an atypical pseudonetwork, anular-granular structures and asymmetrically pigmented follicular ostia. LMM was strikingly diagnosed much more often in darker skinned individuals in our series (90% in tan), showed the lowest Breslow and mitotic indexes (0.41, 1.35 on average, respectively) and exhibited the colour light brown more often than other variants (97.5% *vs* 76.3% for other histologic subtypes)

FIGURE 5

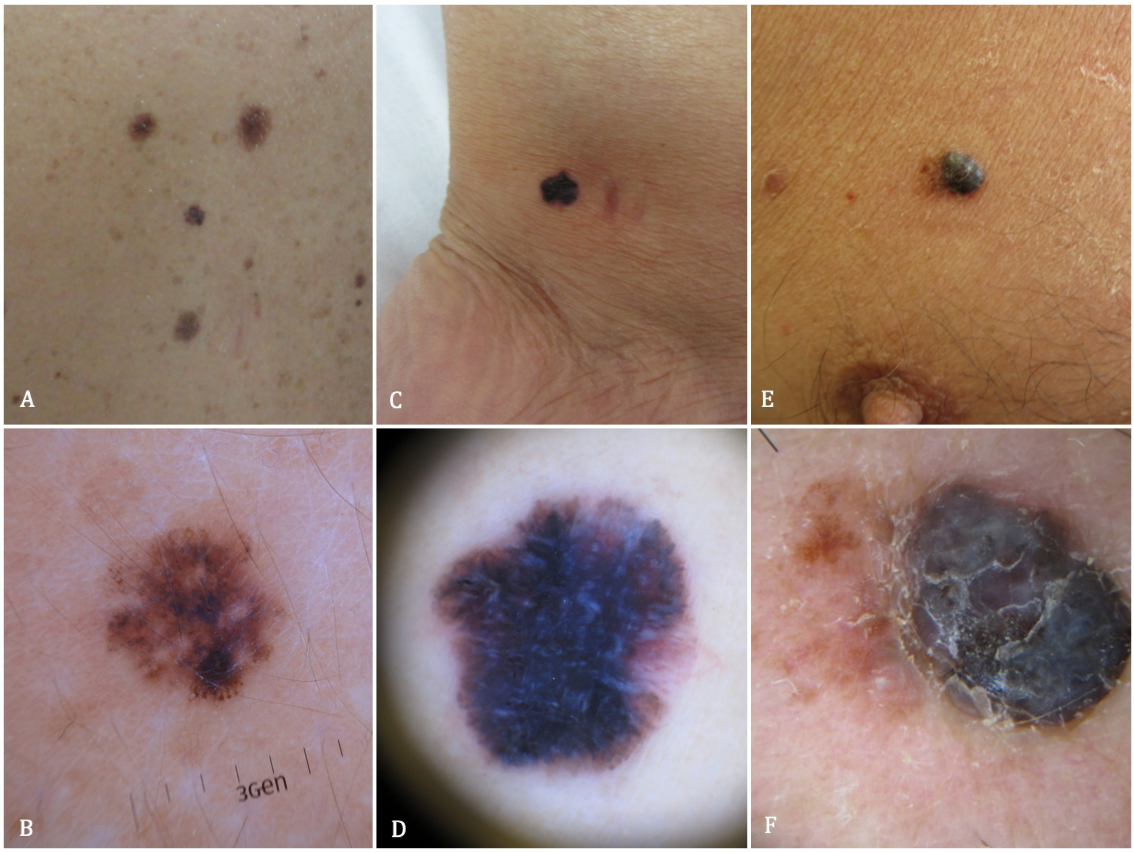

Figure 4: Examples of SSM in tan-skinned patients. A and B correspond to patient #4 (female, 31 years old, SSM on the left scapular area, Breslow 0.5 mm). Dermoscopically, it showed irregular globules, irregular streaks, and peppering-like regression. C and D correspond to patient #8 (female, 56 years old, SSM on the left ankle, Breslow 0.7 mm) showing regular streaks, shiny white streaks, irregular dots, blue-white veil and some milky-red areas containing dotted vessels. E and F correspond to patient #7 (male, 71 years old, SSM on the right breast, Breslow 1.8 mm). Dermoscopically, we saw irregular network, blue-white veil, milky-red areas, and irregular blotches. SSM compared with non-SSM tumours presented more often with colours dark brown (94.8% in SSM *vs* 78.2% respectively) and black (83.6% *vs* 58.2%). Structures significantly associated with SSM were irregular network (50,2% *vs* 20% in non-SSM tumours), irregular globuli (36.2% *vs* 16.4%), irregular streaks (31% *vs* 7.3%), shiny white streaks (24.1% *vs* 9.1%), peppering-like regression (38.8% *vs* 18.2%) and blue-white veil (42.2 *vs* 25.5%).

FIGURE 6

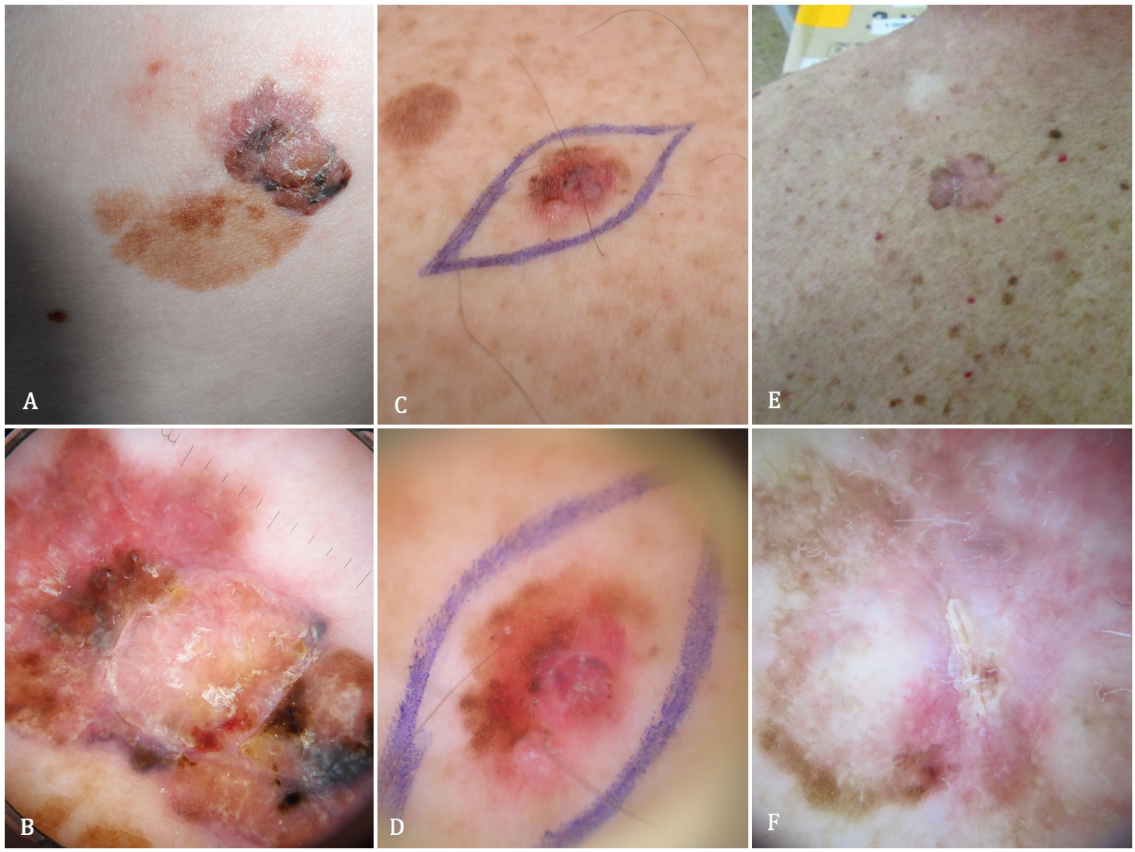

Figure 5: Examples of SSM in sensitive-skinned individuals. A and B correspond to patient #14 (female, 78 years old, SSM on the left scapula, Breslow 2.6 mm). We only see half of the lesion on the dermoscopic picture. There are multiple signs for excision: ulceration, negative network, shiny-white streaks, blue-white veil, milky-red areas, irregular blotches and polymorphous vessels. C and D correspond to patient #13 (male 50 years old, SSM on the left scapula, Breslow 0.9 mm). Dermoscopic signs visible in this lesion are irregular network, shiny-white streaks, milky-red areas and polymorphous vessels. E and F correspond to patient #54 (male, 55 years old, SSM on the left scapula, Breslow 0.4 mm) and exhibited an irregular network, scar-like regression and milky–red areas. Taking only SSM, the colour red was more often seen in sensitive patients (48.6% *vs* 29.1%) and so did also the colour light brown (91.9% *vs* 74.7). Milky-red areas were also more frequently observed in SSM in sensitive-skinned individuals (35.1% *vs* 17.7%).