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Black light visualized solar lentigines on the shoulders and upper back are associated with objectively measured UVR exposure and cutaneous malignant melanoma

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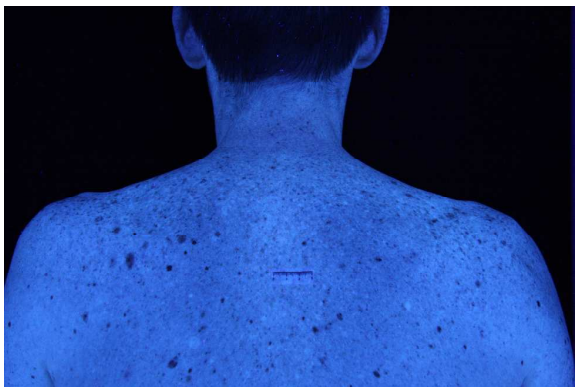
Black light visualized solar lentigines on the shoulders and upper back are associated with high UVR exposure situations and consequently cutaneous malignant melanoma



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ARTICLE TYPE

Black light visualized solar lentigines on the shoulders and upper back are associated with objectively measured UVR exposure and cutaneous malignant melanoma

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Previous studies on the association of solar lentigines with ultraviolet radiation (UVR) exposure have been based on retrospective questionnaires about UVR exposure. We aimed to investigate the association between solar lentigines and UVR exposure in healthy individuals using objective measurements, and to investigate the association between solar lentigines and cutaneous malignant melanoma (CMM). Forty-eight patients with CMM and 48 controls that matched the patients individually by age, sex, constitutive skin type and occupation participated. Solar lentigines on the shoulders and upper back were counted and graded into 3 categories using black light photographs to show sun damage. Current UVR exposure in healthy controls was assessed by personal electronic UVR dosimeters that measured time-related UVR and by corresponding exposure diaries during a summer season. Sunburn history was assessed by interviews. Among controls, the number of solar lentigines was positively associated with daily hours spent outdoors between noon and 3 pm on holidays (P=0.027), days at the beach (P=0.048) and reported number of life sunburns (P<0.001). Compared with matched controls CMM patients had a higher number of solar lentigines (P=0.044). There was a positive association between CMM and higher solar lentigines grade; Category III versus Category I (P=0.002) and Category II versus Category I (P=0.014). Our findings indicate that solar lentigines in healthy individuals are associated with number of life sunburns, as well as time spent outdoors around noon on holidays and beach trips during a summer season, most likely reflecting past UVR exposure, and that solar lentigines are a risk factor for CMM.

Introduction

Solar lentigines are pigmented lesions of the skin histologically characterized by an increase in the number of melanocytes in the epidermis.[1] Previous case-control studies suggest that solar lentigines are associated with increased risk of cutaneous malignant melanoma (CMM).[2-4] Moreover, solar lentigines have been found to be associated with sun exposure[5,6] and sunburns.[5-9] None of these studies have used black light photographs to show additional sun damage.[10] Only interviews or questionnaires have been used to study the association of solar lentigines with UVR exposure behaviour.[5,6,11] It has been shown that individuals maintain their UVR exposure for longer time periods.[12] Accordingly, an association between solar lentigines and current UVR exposure most likely reflects an association between solar lentigines and UVR exposure throughout life.

We aimed to investigate the following: 1. If solar lentigines on the shoulders and upper back are associated with current UVR exposure assessed by objective measurements in healthy individuals without skin cancer; 2. If solar lentigines on the shoulders and upper back are a risk factor for CMM.

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Methods

Study design

This is a case-control study of participants living within 100 km of Bispebjerg Hospital in Copenhagen. The study ran February–September 2009 and March–September 2010. The study was approved by the Committees for Biomedical Research Ethics for the Capital Region in Denmark (H-C-2008-097), and the Declaration of Helsinki protocols were complied with. The participants gave written informed consent.

Participants

The participants were CMM patients and matched controls who had participated in 2009 or 2010 in a case-control study of UVR exposure behaviour and pigmentary traits in CMM patients. The recruitment and exclusion criteria of patients and controls have been described in detail elsewhere.[13]

Controls. Forty-eight participants without skin cancer — in the following referred to as controls — participated. They were recruited from the Danish Central Population Registry, and from employees at the hospital. One control was a friend of a patient with CMM and 5 controls were friends of the authors. The controls matched the patients with CMM individually by sex, age (± 8 years), constitutive skin type measured on the UVR-shielded buttocks, and occupation (mainly indoor work / outdoor work, retired or unemployed).

Patients with CMM. Forty-eight patients with CMM participated. They were recruited from the Department of Dermatology at Bispebjerg Hospital and from private dermatology practice. Twenty-four patients had been diagnosed with CMM during the 7 months preceding study start and 24 patients had been diagnosed from 12 months to 6 years before study start. Thirty-eight patients had superficial spreading malignant melanoma and 10 patients had melanoma in situ. No patient received any medical therapy for CMM during the study.

Photographs in black light of shoulders and upper back

At inclusion in early spring participants had their shoulders and upper back photographed. We used a Canon EOS 40D and a Canon 450D digital camera with an aperture of F:5.6, ISO of 1600, and shutter speed at 1/15. The participants were photographed in a black box with fluorescent tubes (TL08, Philips, Holland) emitting black light. On these photos irregularly shaped solar lentigines larger than 2 mm in diameter were counted in an area of 95 cm^2 on the shoulders and upper back by a physician from the Department of Dermatology. Additionally, solar lentigines were graded into 6 categories (Categories 0-5) based on the density of the solar lentigines on the shoulders and upper back; the score increased with increasing density of the solar lentigines (Fig.1).[14] The grading was performed independently by 2 physicians and 1 bioanalyst, and the median value of these 3 scores was used.

Skin type

Skin type was measured as pigment protection factor (PPF) by an Optimize Scientific Model 555 (Chromo-light, Espergærde, Denmark) that quantifies melanin by diffuse reflectance measurements.[15] PPF equals the number of SED that is predicted to elicit just perceptible erythema (minimal erythema dose) and measures in the range 1–25.[16-18] Constitutive skin pigmentation (PPF on UVR-shielded buttocks), in the following referred to as *C-PPF*, was allowed to vary ± 1.5 between patient and matching control. We also registered self-reported skin type according to Fitzpatrick Classification Scale.[19]

Current UVR exposure behaviour in controls

Personal electronic UVR dosimeter, SunSaver. SunSaver is a personal electronic UVR dosimeter that measures time-stamped UVR doses in standard erythema dose (SED). It measures every 5th second and stores an average of the measurements every 5 min. The dosimeter is mounted in a housing that also contains a digital watch, so that it can be used as a wrist watch.[20] The controls were instructed to wear the SunSaver on their wrist when they were outdoors, at least between 7 am and 7 pm. SunSaver and its calibration are described in detail elsewhere.[21]

UVR exposure diaries. In an UVR exposure diary, the controls were asked to answer "Yes" or "No" to the following questions: (1) Did you wear the SunSaver today? (2) Were you off work or on holiday (away from home during a holiday) today? (3) Did you sunbathe today? (Sitting or lying in the sun with upper body or shoulders exposed to get a tan). (4) Have you used a solarium today? (5) Have you exposed your shoulders or upper body outdoors today? (*e.g.* while working or playing in the garden). (6) Have you applied a sunscreen today? If yes, write factor number and tick which areas had sunscreen applied: head, arms, legs, trunk, shoulders / back. (7) Did you get red from the sun today? For further analysis, body exposure was defined as sunbathing or exposing the shoulders or upper body.

Additionally, controls were interviewed about number of sunburns (sun-provoked redness) throughout life and all participants were asked if they had a home garden.[22]

Data analyzed

One hundred and thirteen participants, comprising CMM patients and controls, had participated in 2009 or 2010 in a case-control study of UVR exposure behaviour and pigmentary traits in patients with CMM.[13,23,24] One patient did not wish to have a black light photograph taken and 1 patient was excluded due to poor quality of the black light photo. From the remaining 111 CMM patients and controls, we constructed 48 pairs each consisting of 1 patient and 1 matched control to analyze for a possible difference in the number of solar lentigines between patients and controls as well as an association between solar lentigines and risk of CMM. Additionally, we analyzed associations between the number of solar lentigines and UVR exposure behaviour among the 48 controls as the CMM patients´ UVR exposure behaviour *after* CMM diagnosis may not be representative of their past UVR exposure behaviour *before* CMM diagnosis.[13,23] Accordingly, associations (if any) between solar lentigines and current UVR exposure behaviour *after* CMM diagnosis will be impossible to interpret. UVR dosimeter and exposure diary data were available from 44 controls. With respect to data from the UVR dosimeter and exposure diary, a control was included for further analysis if there were dosimeter measurements and corresponding diary data for more than 35 days, at least 25 of which were in June, July or August. If, according to the diary, a participant had body exposure but the UVR dosimeter showed 0 SED we considered this an error in filling in the diary. This resulted in 10 days being left out (0.2 % of total days analyzed). A total of 4584 days were analyzed (median 108 days per control).

Statistical analysis

Association between solar lentigines and age, sex and C-PPF. Analyzing all participants as 1 group, we used the Mann-Whitney *U*-test for a difference by sex in the number of solar lentigines and a general linear model for an association between the number of solar lentigines and age and C-PPF.

Association between solar lentigines and current UVR exposure behaviour in healthy controls. Analyzing the group of controls, we aimed to assess whether various measures of current UVR exposure behaviour (assessed by UVR dosimeters and corresponding exposure diaries) and life sunburns were associated with number of solar lentigines using a general linear model for each variable individually, adjusted for age, sex and C-PPF.

Solar lentigines in patients with CMM. To test for a difference between patients and controls we used the Chi squared test for Fitzpatrick skin type, type of home and the gradation of solar lentigines. We used the Wilcoxon matched pairs signed rank sum test for a difference between patients and matched controls in the number of solar lentigines, age and C-PPF. To determine whether solar lentigines was associated with risk of CMM we performed a binary logistic regression analysis adjusting for age, sex, C-PPF, as well as type of home as Danes with a home garden have a higher risk of CMM than those without a home garden.[22] We treated solar lentigines as a categorical variable based on the grading of solar lentigines; the 6 categories of solar lentigines were subsequently merged into 3 categories (the lower Categories

0 and 1 were merged into Category I, the middle Categories 2 and 3 were merged into Category II, and the upper Categories 4 and 5 were merged into Category III) (Fig. 1) which enabled us to compare our results with those from previous studies that have graded solar lentigines into a maximum of 3 categories. Additionally, solar lentigines were treated as a continuous variable based on the count of solar lentigines. The statistical significance limit was P<0.05. We used SPSS 19.0 for Windows (SPSS Inc., Chicago, IL, U.S.A.) for data analysis. Continuous data are presented as median and range (min–max) and categorical data are presented as No. (%).

Results

The baseline characteristics of participants are shown in Table 1. Regarding occupation only 2 participants (1 patient and 1 matched control) of the 96 participants worked outdoors. The rest of the participants worked indoors or were retired or unemployed (data not shown).

Association between solar lentigines and age, sex and C-PPF

Looking at all participants as 1 group, we found that the number of solar lentigines increased with age (regression coefficient, 0.8; 95% confidence interval (CI), 0.4–1.2; P<0.001; R^2=0.151) and decreased with increasing C-PPF (regression coefficient, -7.9; 95% CI, -12.7– -3.2; P=0.001, R^2=0.104). Men had a higher number of solar lentigines than women (median 19.0 in men, 6.5 in women, P<0.001). Taken together in a general linear model increasing age and male sex remained associated with the number of solar lentigines and C-PPF showed a borderline association ([Age: regression coefficient, 0.7; 95% CI, 0.3–1.0; P<0.001], [Sex: regression coefficient, -13.5 for female sex; 95% CI, -23.4– -3.6; P=0.008], [C-PPF: regression coefficient, -4.5; 95% CI, -9.2–0.1; P=0.057], R^2 (model)=0.283). In the following all analyzes are adjusted for sex, age and C-PPF due to the association between solar lentigines and these variables.

Association between solar lentigines and current UVR exposure behaviour in healthy controls

Data from the UVR exposure diaries showed that the number of solar lentigines on the shoulders and upper back was positively associated with number of days at the beach during the observation period (mean, 0.4 lentigines for each day spent at the beach; 95% CI, 0.005–0.8; P=0.048; R^2=0.262). The number of solar lentigines was not associated with number of days off work, on holiday, or with body exposure during the observation period. Data from the UVR dosimeters showed that the number of solar lentigines was positively associated with the daily number of hours spent outdoors between noon and 3 pm on holidays during the observation period (mean, 15.5 lentigines per hour; 95% CI, 1.9–29.1; P=0.027; R^2=0.377). Additionally, there was a borderline significant association between number of solar lentigines and the daily number of hours spent outdoors between noon and 3 pm on holidays with body exposure (mean, 16.1 lentigines per hour; 95% CI, -1.7–34.0; P=0.074; R^2=0.408). We found no association between the number of solar lentigines and time spent outdoors between noon and 3 pm on workdays, on days off work, or on all days with body exposure. The number of solar lentigines was positively associated with reported number of life sunburns in controls; (mean, 0.3 lentigines for each sunburn; 95% CI, 0.1–0.4; P<0.001; R^2=0.388) (Table 2).

Solar lentigines in patients with CMM

There was no difference between patients and matched controls in sex, age, C-PPF or Fitzpatrick skin type due to matching (Table 1). A higher percentage of patients lived in a home with a garden compared with controls although this difference was not statistically significant (P=0.080). Patients had a higher number of solar lentigines on the shoulders and upper back (median 12.5 in patients with CMM, 6.5 in controls, P=0.044) and were more often classified with solar lentigines in the upper Categories II and III compared with matched controls (P=0.003) (Table 1).

In a binary logistic regression analysis there was a significant positive association between solar lentigines grade and CMM when treating solar lentigines as a categorical variable; Category III versus Category I (OR=13.05; 95% CI, 2.54─67.09; P=0.002) and Category II versus Category I (OR= 3.59; 95% CI, 1.25─9.94, P=0.014) (Table 3). However, the number of solar lentigines was not significantly associated with CMM when it was treated as a continuous variable (odds ratio (OR)=1.01; 95% CI, 0.99─1.04; P=0.184).

Discussion

In this case-control study we found that the number of solar lentigines on the shoulders and upper back — counted on black light photographs to show sun damage — was associated with hours spent outdoors daily between noon and 3 pm on holidays and number of days at the beach during a summer season, as well as reported number of life sunburns in healthy controls without skin cancer. Patients with CMM had a significantly higher number of solar lentigines on the shoulders and upper back compared with matched controls. Solar lentigines in the higher Category II and III, based on the density of the lesions, were associated with higher risk of CMM.

The study had important strengths. We graded and counted the number of solar lentigines on the shoulders and upper back using black light photographs as it is suggested that black light photographs show additional sun damage not visible in visible light.[10] Current UVR exposure behaviour in healthy controls was assessed by objective measurements (UVR dosimetry and questions about UVR exposure behaviour answered daily in an exposure diary during a summer season), which reduced the risk of recall bias. The long observation period enabled us to study a large number of work days and days off work or on holiday. Patients and controls were matched individually by age, sex, constitutive skin type and occupation (1 control per patient) to ensure that any possible difference in the number of solar lentigines between patients and matched controls was not affected by differences in these characteristics between the two groups.

The study was mainly limited by sample size, and the possibility of type I and type II errors cannot be excluded. Hence, we may have obtained statistically significant results that are "false positive" and non significant results that are "false negative". We must acknowledge that the study may be underpowered regarding the statistically significant associations of number of solar lentigines with number of days at the beach (observed power=0.51) and hours spent outdoors / day between noon and 3 pm on holidays (observed power=0.32). However there was a strong power for the association of number of solar lentigines with number of life sunburns (power=0.96). Also, we may have attracted both patients and controls with special sun habits.[23] Patients and controls in the current study may not be representative of the CMM population or the general population respectively.

The quality of the dosimeter and diary data depended on the participants wearing the dosimeter and filling in the diary each day. Nonetheless, a previous study based on personal electronic UVR dosimeters and UVR exposure diaries has shown high participant compliance and data reliability.[25] Regarding the black light photographs, moles may have been misclassified as solar lentigines. To overcome this, pigmentary changes were only classified as solar lentigines if they were irregularly shaped. Ten patients had CMM in situ whereas 38 patients had superficial spreading CMM, although there was no significant difference in the number of solar lentigines between these 2 groups of patients.

The first question we asked was whether the number of solar lentigines on the shoulders and upper back was associated with objectively measured current UVR exposure. Knowing that individuals maintain their UVR exposure behaviour for longer time periods,[12] an association between solar lentigines and current UVR exposure most probably reflects an association between solar lentigines and UVR exposure throughout life. CMM patients are likely to have changed their UVR exposure behaviour, at least immediately after diagnosis.[13,24] Additionally, CMM patients may be affected by recall bias regarding UVR exposure behaviour before CMM diagnosis, although there is some disagreement on this matter, especially regarding sunbathing and sunburns.[26-28] Hence, solar lentigines in patients with CMM cannot be expected to associate with current or past UVR exposure. Consequently, we limited our analyzes of the association of current UVR exposure behaviour (assessed by personal electronic UVR dosimeters and UVR exposure diaries) and reported number of life sunburns with solar lentigines, to include only the group of healthy controls. The positive association between solar lentigines and life sunburns among controls corresponds with the findings from previous studies,[6-8,11] and suggests that solar lentigines are a measure of UVR-induced skin damage. Among controls, we found significantly positive associations between the number of solar lentigines and time spent outdoors around noon during holidays (as well as a borderline significant association with time spent outdoors around noon during holidays with body exposure), and number of days at the beach. A previous study of UVR exposure behaviour among Danes based on UVR dosimetry and exposure diaries has shown that 50 % of the daily UVR dose is received around noon, and that subjects expose themselves to high UVR doses on holidays, at the beach, and on days with body exposure.[29] Accordingly, holidays, days at the beach and days with body exposure are high exposure days. In the present study, however, the UVR dose in connection with these behaviours was not associated with the number of solar lentigines, which could be due to the limited sample size.

The next question we asked was whether solar lentigines on the shoulders and upper back were associated with CMM. We found that patients had more solar lentigines than matched controls both in number as well as a higher grade. In a binary logistic regression model, repealing the individual matching between patients and controls, and treating solar lentigines as a categorical variable, solar lentigines in the upper Categories II and III were associated with increased risk of CMM compared with solar lentigines in the lower Category I, which is consistent with findings from previous studies.[2-4] However, we found no significant association between the number of solar lentigines and CMM when solar lentigines were treated as a continuous variable. Accordingly, there was no linear relation between solar lentigines and risk of CMM. To determine if the number of life sunburns could explain this lack of linearity we added number of life sunburns to the model, however this did not change our findings (data not shown). We speculate if the risk of CMM stabilizes for a certain number of solar lentigines.

Conclusions

The findings from the present study indicate the following: The number of solar lentigines on the shoulders and upper back is associated with current UVR exposure on high exposure days in terms of time spent outdoors around noon on holidays and beach trips, as well as reported life sunburns among healthy controls; Patients with CMM have significantly more solar lentigines compared with matched controls, most likely owing to past high UVR exposure. Moreover, a higher grade of solar lentigines on the shoulders and upper back is associated with a higher risk of CMM. However, studies on a larger population are needed to make any further conclusions.

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Table 1. Baseline characteristics of participants at study start. Controls matched the CMM patients by sex, age, constitutive PPF and occupation at study start

	CMM patients N=48	Controls N=48	P value
Men / Women, No. (%)	16 (33) / 32 (67)	16 (33) / 32 (67)	1.0*
Age at study entry, years, median (range)	40 (26–70)	36.5 (27–73)	0.438**
Skin type (Fitzpatrick), No. (%)			
I / II	12 (25) / 18 (38)	5 (10.5) / 25 (52)	
III / IV	14 (29) / 4 (8)	13 (27) / 5 (10.5)	0.260*
Constitutive PPF, median (range)	4.0 (2.5–7.1)	4.4 (3.2–6.3)	0.109**
Living in a home with a garden, No. (%)	20 (42)	11 (23)	0.080*
Counted number of solar lentigines, median (range)	12.5 (0–127)	6.5 (0–117)	**0.044****
Gradation of solar lentigines, No. (%)			
Category I	10 (21)	25 (52)	
Category II	26 (54)	19 (40)	
Category III	12 (25)	4 (8)	**0.003***

Abbreviations: PPF, pigment protection factor; CMM, cutaneous malignant melanoma. P values less than 0.05 are shown in bold typing.
*P value calculated using the Chi squared test.
** P value calculated using the Wilcoxon matched pairs signed rank sum test.

Table 2. Association between solar lentigines and UVR exposure behaviour in healthy controls calculated in a general linear model for each variable individually adjusting for sex, age and constitutive PPF

Diary and dosimeter variables, N=44			
No. of days	**Median (range)**	**Regression coefficient (95% CI)**	**P value**
Work days	46.5 (0–89)	-0.02 (-0.3–0.3)	0.921
Off work	41.5 (17–118)	0.12 (-0.1–0.4)	0.328
On holiday (away from home during a holiday)	11.5 (0–48)	-0.4 (-1.0–0.3)	0.284
With body exposure (sunbathing or exposing shoulders or upper body)	14.5 (0–97)	0.1 (-0.4–0.5)	0.786
On holiday with body exposure	2.5 (0–21)	-0.2 (-1.4–1.0)	0.697
At the beach	4.5 (0–98)	0.4 (0.005–0.8)	**0.048**
Mean hours spent outdoors / day between noon and 3 pm	**Median (range)**	**Regression coefficient (95% CI)**	**P value**
Workdays	0.4 (0–1.4)	11.6 (-12.7–35.9)	0.337
Off work	1.0 (0.5–1.8)	14.9 (-5.0–34.8)	0.139
On holiday	1.4 (0–2.3)	15.5 (1.9–29.1)	**0.027**
With body exposure	1.6 (0.7–2.8)	4.0 (-11.9–19.9)	0.614
On holiday with body exposure	1.8 (0.8–3.0)	16.1 (-1.7–34.0)	0.074
No. of life sunburns (sun-provoked redness), N=48	28 (2–200)	0.3 (0.1–0.4)	**<0.001**

Abbreviations: UVR, ultraviolet radiation; PPF, pigment protection factor; CI, confidence intervals. P values less than 0.05 are shown in bold typing.

Table 3. Association between CMM and solar lentigines calculated in a binary logistic regression model adjusting for age, sex, constitutive PPF and type of home. Controls matched the CMM patients by sex, age, constitutive PPF and occupation at study start

Solar lentigines	OR (95% CI)	P value
Counted number	1.01 (0.99─1.04)	0.184
Gradation		
Category I (baseline)	1	-
Category II	3.59 (1.30─9.94)	**0.014**
Category III	13.05 (2.54─67.09)	**0.002**

Abbreviations: PPF, pigment protection factor; CMM, cutaneous malignant melanoma; OR, odds ratio; CI, confidence intervals.
The variable solar lentigines was treated both as a continuous variable based on the count of solar lentigines and as a categorical variable based on the grading of solar lentigines. P values less than 0.05 are shown in bold typing.

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Fig. 1. Black light photograph of upper back and shoulders. Irregularly shaped solar lentigines larger than 2 mm in diameter that were visible on the black light photographs were counted in an area of 95 cm^2 on the shoulders and upper back. Moreover, solar lentigines were treated as a categorical variable based on the grading of solar lentigines[14]; the 6 categories of solar lentigines were subsequently merged into 3 categories (the lower Categories 0 and 1 were merged into Category I, the middle Categories 2 and 3 were merged into Category II, and the upper Categories 4 and 5 were merged into Category III).