ANTICANCER RESEARCH *40*: 557-564 (2020)
doi:10.21873/anticanres.13985

Lifetime UVR Dose and Skin Cancer Risk, Determined by Their Common Relation to Solar Lentigines

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Abstract. *Background/Aim: Ultraviolet radiation (UVR) causes solar lentigines (SL) and skin cancer (SC) in humans. The association between measured lifetime UVR dose and SC has not been investigated. This study investigated this relation through their common relationship to SL. Materials and Methods: First we investigated the association between lifetime UVR dose and SL for 16,897 days in 38 healthy participants, and secondly, the relation between SL and SC was investigated in 2,898 participants, including 149 with SC. By combining both studies, SC risk related to lifetime UVR dose and skin phototype was estimated. Results: A positive association was found between SL and lifetime UVR dose (p=0.060). Skin phototype (p=0.001) and SL (p<0.001) were associated with SC. Combined SC risk increased 1.23 by doubling the average lifetime UVR dose and was 34.9 times higher for those with very fair skin compared to dark Mediterranean skin. Conclusion: The estimate of SC risk shows that skin phototype is of greater relative importance than lifetime UVR dose.*

Ultraviolet radiation (UVR) is a key factor in the development of skin cancer (1,2). The strongest evidence of this association is derived from animal studies (3, 4), in-vitro studies on human cells (5), and from epidemiological studies (1, 6). A direct examination of the association between UVR and skin cancer is a challenging task, as it is not feasible to conduct a prospective study with objectively measured UVR exposure over several decades, waiting for skin cancer to develop.

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Key Words: Skin cancer, UVR, solar lentigines, skin phototype.

UVR (7-12) and skin cancer, both basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and cutaneous malignant melanoma (CMM) (7, 8, 12), are seemingly associated with solar lentigines. Solar lentigines are acquired pigmented lesions and considered to be a sign of photodamage (8, 13). The common relation between solar lentigines and UVR, and between lentigines and skin cancer provides a unique opportunity to investigate the association between UVR and skin cancer.

Excessive UVR of the skin disturbs the pigment distribution and can result in dark, irregular, edge-freckled spots. Histologically, solar lentigines are characterised by a locally increased number of melanocytes in the epidermis (7 ,8, 13, 14). Some solar lentigines are invisible to the naked eye and in traditional photographs. However, containing more melanin than the surrounding skin, they become visible in black light due to its absorption by melanin (13, 14). Solar lentigines are strongly associated with age (8, 13, 15-17), and are predominantly found on sun-exposed body areas (8, 15, 16, 18), which suggests that increased UVR exposure throughout life, not age alone, is essential for the development of solar lentigines.

The present study is divided into three parts: (i) The association between objectively measured UVR dose and solar lentigines; (ii) the association between solar lentigines and skin cancer; and (iii) a combination of the above to calculate skin cancer risk due to UVR.

The combining of two data materials is an approach with limitations, but it provides an alternative way to examine the association between skin cancer and objectively measured UVR dose.

Materials and Methods

UVR dose and solar lentigines. Data source. The association between individual UVR dose and solar lentigines was examined using a longitudinal study where UVR dose was measured for 38 individuals for 2-5 summers between 1999 and 2012 (19-21). Details of the individual participation year are given in Table I.

Table I. *Characteristics of the participants in the UVR study subdivided into male and female participants.*

	No.	Age in 2012, years	Facial solar lentigines grade	Yearly estimated UVR dose*, mean	Lifetime UVR dose*	Yearly intermittent days, mean	Year of participation				
							1999	2000	2001	2006	2012
Male participants	1	69	3.33	71	4,899	14.8	x	x	x	x	x
	2	43	4.00	95	4,085	9.0	x	-	x	x	x
	3	46	3.67	118	5,428	13.4	x	x	x	x	x
	4	66	3.00	137	9,042	13.6	x	x	x	x	x
	5	54	3.67	138	7,452	10.8	x	x	x	x	x
	6	58	3.50	146	8,468	9.0	x	x	x	x	x
	7	42	2.33	165	6,930	14.0	x	x	x	x	x
	8	31	2.33	225	6,975	11.0	x	-	-	-	x
	9	71	4.33	293	20,803	10.8	-	x	x	x	x
	10	30	3.00	352	10,560	9.5	x	-	-	-	x
	11	52	3.67	384	19,968	2.8	-	x	x	x	x
	12	76	4.50	419	31,844	7.0	x	x	-	x	x
	13	68	3.67	482	32,776	10.8	-	x	x	x	x
	14	64	4.50	629	40,256	11.5	-	x	x	x	x
Female participants	15	50	3.33	34	1,700	9.0	x	-	-	x	x
	16	77	4.33	51	3,927	16.7	x	-	-	x	x
	17	64	4.33	64	4,096	9.8	x	x	x	x	x
	18	51	5.00	75	3,825	11.0	x	-	-	x	x
	19	66	4.00	77	5,082	13.6	x	x	x	x	x
	20	38	2.67	82	3,116	13.0	-	x	x	x	x
	21	29	3.67	106	3,074	11.5	x	-	-	-	x
	22	69	3.33	111	7,659	13.0	-	x	x	-	x
	23	56	4.00	113	6,328	12.7	-	x	-	x	x
	24	40	2.33	126	5,040	11.0	x	x	x	x	x
	25	37	4.00	161	5,957	13.0	x	-	-	x	x
	26	30	5.00	165	4,950	9.0	x	-	-	-	x
	27	30	3.00	171	5,130	10.5	x	-	-	-	x
	28	46	3.33	172	7,912	13.4	x	x	x	x	x
	29	31	4.33	172	5,332	9.5	x	-	-	-	x
	30	30	1.67	206	6,180	13.5	x	-	-	-	x
	31	32	3.67	215	6,880	12.5	x	-	-	-	x
	32	49	2.50	220	10,780	9.8	x	x	x	x	x
	33	69	4.00	231	15,939	7.6	x	x	x	x	x
	34	41	3.33	232	9,512	10.6	x	x	x	x	x
	35	38	3.33	260	9,880	10.3	-	x	-	x	x
	36	29	3.33	309	8,961	14.0	x	-	-	-	x
	37	49	2.67	399	19,551	15.0	-	x	-	x	x
	38	67	4.33	401	26,867	11.7	x	-	-	x	x
	Mean	50	3.55	205	10,452	11.3					
	Min	29	1.67	34	1,700	2.8					
	Max	77	5.00	629	40,256	16.7					

*Standard erythema dose.

Measurements of UVR dose. During the study period participants wore a personal, electronic wrist-borne UVR dosimeter, SunSaver (22) which provided time-stamped UVR doses measured as standard erythema dose (SED). Each SunSaver was individually calibrated to measure every 8th second and to store the average of the measurements every 10th minute (19, 22). For each participant, an estimated yearly UVR dose was calculated based on both individual and ambient daily doses. For days without measurements, the same proportion of ambient UVR as on comparable days was used, accounting for whether the participant was in Denmark, abroad, at work or off work. Ambient UVR was measured with a UV biometer Model 501 (Solar Light Co. Inc., Glenside, PA, USA) mounted on the roof of Bispebjerg Hospital in Copenhagen, Denmark. Further details are described elsewhere (19, 20, 22). To obtain a measure of lifetime UVR dose, the mean estimated yearly UVR dose was multiplied by the participant's age in 2012. Furthermore, an objective measure of intermittent sun exposure introduced by Bodekær *et al*. (23) was used. The mean of intermittent days throughout the study period was subsequently multiplied by the participant's age to calculate a lifetime measure of intermittent sun exposure (lifetime intermittent days).

Solar lentigines and skin cancer. Data source. The association between solar lentigines and skin cancer was investigated using data of 4,177 individuals from a cross-sectional study carried out in 2011. All visited a walk-in bus located at various, primarily sunny, locations in Denmark (24).

Skin cancer. The participants completed a questionnaire in which they stated if a physician had ever diagnosed them with CMM, BCC, or SCC. Answers from all the participants were validated through The Danish Pathology Data Bank (n=2,898). A total of 149 participants had previously had histologically confirmed skin cancer; 116 had been diagnosed with BCC/SCC, 36 had been diagnosed with CMM, and three of these had been diagnosed with both. Further details on the validation are described elsewhere (25).

Solar lentigines. All participants underwent black-light photography of their facial solar lentigines taken by a Canon EOS REBEL XS with NT24EX UVR flash (Unit-one, Birkeroed, Denmark). Subsequently, the photos were assessed independently by three staff members from the Department of Dermatology at Bispebjerg Hospital. The photos were graded based on the density of lentigines portrayed in six illustrations, previously used by Dubin *et al*. (26) with 0 (no lentigines) being the lowest grade and 5 being the highest grade. A mean of the three gradings was used for each participant.

Skin phototype. Skin phototype was measured objectively as pigment protection factor (PPF) with an Optimize Scientific B558 (Chromo-Light, Vedbæk-DK) (27-29). PPF quantifies melanin by diffuse reflectance measurements and is expressed as the number of SED needed to elicit just perceptible erythema. In the study of the association between solar lentigines and UVR, constitutive PPF was measured on buttocks previously unexposed to UVR, but in the study of solar lentigines association with skin cancer, it was not possible to measure PPF on the buttocks. Therefore, PPF on the inside of the upper arm was measured and converted into buttocks PPF (*via* pigmentation) using the following formula (30):

$$\textit{Predicted buttocks pigmentation} = \frac{\textit{Observed pigmentation on the inside of the upper arm}}{1.52+0.0056\times\text{age}}$$

Statistical analyses. Solar lentigines grade was generally considered a continuous variable but was considered as a categorial variable when comparing lentigines grades for individuals with and without skin cancer, using Pearson's chi-square test (Figure 1). The Mann–Whitney *U*-test was used to compare solar lentigines grade and UVR dose between individuals with and without skin cancer and between men and women. Binary logistic regression was used for analysing the probability of skin cancer, using age-weighting to match the Danish age composition in 2011 (Statistics Denmark, www.dst.dk). A balanced sensitivity and specificity were calculated as the analysis was not concerned with diagnostic accuracy. The general linear model (analysis of variance) was used to analyse the association between solar lentigines, lifetime UVR dose and PPF. To explore the best relation between lifetime UVR dose and solar lentigines grade, the following models were tested: Linear, logarithmic, inverse, quadratic, power, S-curve and exponential.

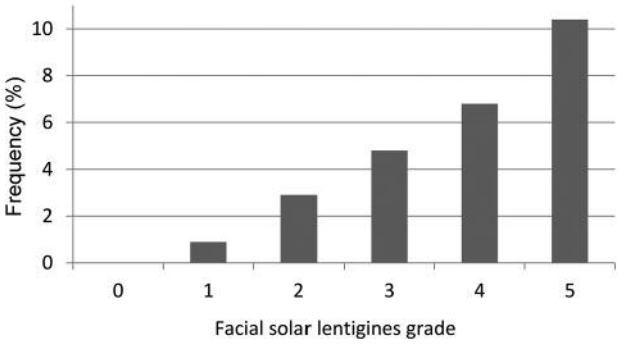

Figure 1. *Percentage of individuals with skin cancer for different grades of facial solar lentigines (rounded up) in the study on the association between solar lentigines and skin cancer.*

IBM SPSS Statistics for Windows (Version 22.0; IBM, Armonk, NY, USA) was used for all statistical analyses, all tests were two-sided, and a *p*-value of 0.05 was considered significant.

Results

UVR dose and solar lentigines. On average, the 38 participants wore the SunSaver for 121 days each participation year (range=87-148 days), and a total of 16,893 days were analysed. Further details on participant characteristics are shown in Table I.

The association between lifetime UVR dose and facial solar lentigines was dependent on sex. While there was no significant difference between men and women for facial solar lentigines (mean grade of 3.5 and 3.6, respectively, p=0.981), men had a significantly higher mean lifetime UVR dose than women (14,959 SED and 7,822 SED, respectively, p=0.029). For men there was a borderline significant positive association (p=0.060) between lifetime UVR dose and facial solar lentigines best explained by a power model with an R2 value of 0.265, as seen in Table II. Figure 2 shows a graphic representation of the association. For women the association was not significant (p=0.706).

Lifetime intermittent days were not significantly associated with facial solar lentigines for either men or women (p=0.626 and p=0.484, respectively). PPF was borderline positively associated with facial solar lentigines (p=0.090) but not associated with lifetime UVR dose (p=0.252).

Facial solar lentigines and skin cancer. Individuals without skin cancer had a significantly lower facial solar lentigines grade (mean=2.82) than individuals with skin cancer (mean=3.51) (p<0.001). No individuals with facial solar lentigines grade 0 had skin cancer and the percentage with skin cancer increased significantly with increasing grade of solar lentigines (p<0.001) (Figure 1).

Table II. *General linear model for the association between lifetime UVR dose and facial solar lentigines, for men.*

	Ln (facial solar lentigines)		
	Beta value	*p*-Value	R^2
Ln (lifetime UVR dose)	0.142	0.060	0.265

Ln (solar lentigines)=–0.079+0.142 × Ln (lifetime UVR dose)

There was a significant positive association between grade of facial solar lentigines and skin cancer with an odds ratio of 1.824 ($p<0.001$). Furthermore, PPF was significantly inversely associated with skin cancer ($p=0.001$). Accordingly, the association between facial solar lentigines and skin cancer was adjusted for PPF. The adjusted model had a sensitivity of 66% and a specificity of 66%. Detailed information is shown in Table III.

The range in solar lentigines grade was 0-5 and the range in PPF in the data material was approximately 1-9. Based on the adjusted model shown in Table III, an individual with grade 5 facial solar lentigines would have an odds ratio of 20 for having skin cancer compared to an individual with grade 0 ($1.824^{5-0}=20$). Furthermore, an individual with a PPF value of 1 would have an odds ratio of 35 for having skin cancer compared to an individual with a PPF value of 9 ($0.641^{1-9}=35$).

UVR dose and skin cancer. The two models defined above were combined in one equation for the association between UVR dose and skin cancer, using the beta-values generated by the models described in Tables II and III. As the association between lifetime UVR dose and solar lentigines was present only for men, the model solely includes men.

Table IV shows the odds ratio values for skin cancer risk based on lifetime UVR dose and PPF using the generated model. The odds ratio of skin cancer in Table IV is exemplified with PPF values from 1 to 9 and lifetime UVR doses ranging from 1,500 SED to 48,000 SED as these approximately correspond to the range in the presented data. The skin cancer risk was 2.71 times higher for an individual with a lifetime UVR dose of 48,000 SED compared with one with a dose of 1,500 SED, considering all body sites. Doubling the average lifetime UVR dose increases skin cancer risk by 1.23. The skin cancer risk was 34.9 times higher for an individual with a PPF of 1 than for an individual with a PPF of 9. Based on the equation provided in Table IV, every comparison of PPF and lifetime UVR dose can be calculated.

We recalculated the skin cancer risk including only skin cancer occurring on the face or forearms, since these locations are usually not covered by clothes when people expose themselves to the sun. In this way, the measured UVR dose to skin where skin cancer commonly occurs is more correct. By doing so, the skin cancer risk was 3.68 times higher for an individual with a lifetime UVR dose of 48,000 SED compared with one with a dose of 1,500 SED, while it was 14.6 times higher for an individual with a PPF of 1 than for an individual with a PPF of 9 (Table IV).

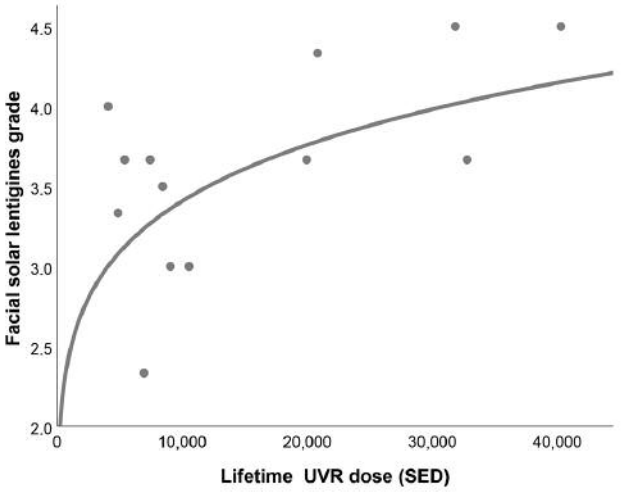

Figure 2. *The association between lifetime UVR dose and facial solar lentigines grade for men in the study of solar lentigines and lifetime UVR dose in standard erythema dose (SED).*

Discussion

In the present study, an association between skin cancer risk and lifetime UVR dose was determined through their common relation to solar lentigines. Calculations showed that skin cancer risk increased with increasing lifetime UVR dose and decreasing PPF.

Facial solar lentigines grade was positively associated with skin cancer. A study by Idorn *et al.* using black light photography to visualise shoulder solar lentigines found solar lentigines to be positively associated with CMM (7), which supports the findings in the present study. The vast majority of studies examining solar lentigines and skin cancer do not use black light photography to visualise solar lentigines (8-12, 31-40). As solar lentigines invisible to the naked eye become apparent in black light, it is likely that the number of solar lentigines has been underestimated in most studies, leading to biased results.

As expected, PPF was inversely associated with skin cancer risk (41).

For men, there was a borderline significant association between facial solar lentigines and lifetime UVR dose, but not for lifetime intermittent days. Bastiaens *et al.* found cumulative UVR dose to be associated with facial solar lentigines but not with intermittent sun exposure (8), while Monestier *et al.* found intermittent sun exposure to be

Table III. *Binary logistic regression for the association between skin cancer and facial solar lentigines, both simple and adjusted for skin phototype (PPF).*

		p-Value	Beta value	Odds ratio	95% CI
Simple model*	Facial solar lentigines	<0.001	0.632	1.880	1.565-2.259
Adjusted model**	Facial solar lentigines	<0.001	0.601	1.824	1.494-2.227
	PPF	0.002	–0.444	0.641	0.492-0.836

CI: Confidence interval. **Logit(P)*=–5.014+0.632 × solar lentigines grade. ***Logit(P)*=–3.212+0.601 × solar lentigines grade+PPF × (–0.444).

Table IV. *Modelled odds ratio values for risk of skin cancer based on lifetime UVR dose and skin phototype (PPF), adjusted by age for the Danish population.*

		Estimated lifetime UVR dose (SED)					
	PPF	1,500	3,000	6,000	12,000	24,000	48,000
All skin cancer types and all body sites (A)	9	1*	1.18	1.41	1.71	2.13	2.71
	7	2.43	2.86	3.42	4.17	5.18	6.59
	5	5.91	6.95	8.31	10.1	12.6	16.0
	3	14.4	16.9	20.2	24.6	30.6	38.9
	1	34.9	41.0	49.1	59.8	74.4	94.6
All skin cancer types on face and forearm (B)	9	1*	1.24	1.56	2.02	2.69	3.68
	7	1.95	2.42	3.05	3.95	5.25	7.19
	5	3.82	4.72	5.96	7.72	10.3	14.1
	3	7.46	9.23	11.7	15.1	20.1	27.5
	1	14.6	18.0	22.8	29.5	39.2	53.7

SED: Standard erythema dose. *Reference category (P_0). Odds ratios were calculated based on the following equation:

$$\text{Odds ratio} = \frac{e^{logit}(P_1)}{e^{logit}(P_0)} ,$$

A: *Logit(P)*=–3.212+0.601 × [$e^{-0.079}$ × (Lifetime UVR dose$^{0.142}$)]+PPF × – 0.444,
B: *Logit(P)*=–5.159+0.785 × [$e^{-0.079}$ × (Lifetime UVR dose$^{0.142}$)]+PPF × – 0.335.

associated with facial solar lentigines but not with cumulative UVR dose (11). These different results might be due to different approaches in the assessment of solar lentigines or the quantification of sun exposure.

Our analyses showed no difference in solar lentigines grade between men and women but a significant difference in lifetime UVR dose. We examined whether the difference was due to age or distribution of yearly UVR dose, or more men than women being outdoor workers. However, these factors were only borderline significantly different (p=0.087, p=0.161 and p=0.052, respectively), although the male participants were 8 years older than the female participants (mean of 55 and 47 years, respectively). There was a smaller span of yearly UVR doses for women compared to men (34-401 SED and 71-629 SED, respectively), which would make it much more difficult to show a clear relation between UVR dose and lentigines in women than in men.

Previous studies have shown either no association between skin phototype and solar lentigines (8, 15), or, more surprisingly, a positive association (11), the latter contrasting strongly with other UVR-induced skin damage such as skin cancer and actinic keratosis. We found a borderline significant interaction between PPF and solar lentigines, which may be explained by self-regulative behaviour. People with very fair skin (PPF 1-2) simply expose themselves less to the sun (42), thereby possibly developing fewer solar lentigines.

Study strengths and limitations. A substantial strength of the present study was the use of objective data and black light photographs to visualise solar lentigines. The longitudinal study design used for examining UVR dose and solar lentigines is of further support to the study.

Individuals with skin cancer generally have a higher solar lentigines grade than individuals without skin cancer, which

both the present study (ii) and previous studies (7, 24) have shown. In the study of lifetime UVR and solar lentigines, only individuals without skin cancer were included to ensure that skin cancer would not influence the relationship with UVR dose. Thus, individuals with the highest number of solar lentigines did not participate in the present study, which possibly led to underestimation of the association between UVR dose and solar lentigines. Furthermore, the association between solar lentigines and skin cancer was investigated using cross-sectional data, making the conclusion of a causal relation impossible. However, the fact that there is an association is unquestionable.

Despite a clear indication of an association between lifetime UVR dose and facial solar lentigines, the association was borderline significant. This was most likely due to the small number of individuals (14 men out of 38 participants) included in the analysis. Even though this was a limitation, the data from each of these 14 individuals is very comprehensive. Previous finding of solar lentigines predominantly on sun-exposed body sites (8, 15, 16, 18) and a significant association between lifetime UVR dose in previous studies (7-12) further strengthens the assumption of the relationship. Moreover, within the data material, an association between lifetime UVR dose and solar lentigines on the shoulders were subsequently investigated, showing similar results for facial and shoulder solar lentigines (UVR dose and shoulder lentigines: p=0.024), which strengthens the hypothesis of the relationship between UVR dose and solar lentigines.

To estimate lifetime measurements of UVR dose, the mean of the yearly estimated UVR doses was multiplied by the individual participant's age, which may have caused uncertainty in the estimates. Life stages (childhood, adulthood, retirement) may have different influence on the amount of sun exposure (19, 21). One study has shown that regardless of skin cancer status, individuals maintain their sun behaviour over time (43), indicating that sun exposure behaviour is a relatively resilient pattern of behaviour which most likely does not change very much during a person's lifetime. The participants in the present UVR study, including individuals with a low, medium, and high sun exposure, did not change their sun exposure pattern throughout the years of participation (p=0.431).

Furthermore, people with fairer skin phototypes possibly used sun protection to a larger extent than people with a darker skin phototype. However, in the present study, there was no association between days with sun protection and PPF (p=0.319).

To obtain an indication of the extent to which the final model generated can be used as a realistic estimate of skin cancer risk in the Danish population, the prevalence of skin cancer in the Danish population was compared to the probability of skin cancer for an 'average Dane'.

In 2011 (the same year as the skin cancer information was obtained), the prevalence of CMM was 21,513 and the prevalence of keratinocyte skin cancer (both BCC and SCC) was 121,649 (44) For the entire Danish population of 5,570,572 individuals (44), the probability of skin cancer was estimated at 2.57%. In our dataset 149 out of 2,898 had skin cancer, corresponding to 5.14%, indicating that our study attracted more people with skin cancer (45).

To determine the skin cancer risk for an 'average Dane' the following three values were inserted into the model: Mean age of the Danish population (40.4 years) (46); mean yearly estimated UVR dose from the UVR part of the study (205 SED), which is the best estimate of the average Danish UVR dose; and mean PPF (4.1) of the entire population from the second part, which is the best estimate of the average PPF. Based on these values, the probability of skin cancer for an average Dane was estimated at 4.40%.

The two probabilities, 4.40% and 2.57%, are not the same, but the numbers are still comparable, which strengthens the assumption that the model can be used to estimate skin cancer risk in the Danish population by taking both UVR dose and skin phototype into account.

As intermittent sun exposure was not significantly related to solar lentigines in our study, we made a model including only skin cancer on forearms and face representing sites chronically exposed to the sun (Table IV). This model shows the same relationship as the model for all skin cancer in Table IV; skin phototype is more important than lifetime UVR dose, but less pronounced than in model A with all skin cancer.

Conclusion

A method combining two sets of data provided us with important data on skin cancer risk related to objectively measured UVR exposure and objectively measured skin phototype.

To the best of our knowledge, this is the first study investigating skin cancer risk based on objectively measured sun exposure. Our findings suggest that PPF is of greater relative importance than lifetime UVR dose for skin cancer risk.

Conflicts of Interest

There are no conflicts of interest to declare.

Authors' Contributions

Ann-Sofie Sonne Holm-Schou: Formulation/identification of the scientific problem, design of the work, conduction of the analysis, drafting of the work and interpretation of data. Peter Alshede Philipsen: Formulation/identification of the scientific problem, design of the work, interpretation of the analysis, revising the work critically for important intellectual content. Luise Winkel Idorn: Grading of the lentigines photos and revising the work critically for important intellectual content. Elisabeth Thieden: Acquisition of the data for part (i) of the study and revising the work critically for important intellectual content. Hans Christian Wulf: Formulation/identification

of the scientific problem, design of the work, interpretation of the analysis, revising the work critically for important intellectual content, obtaining funding.

Acknowledgements

Financial support: This study was funded by The LEO Foundation.

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Received October 7, 2019
Revised October 28, 2019
Accepted October 29, 2019