Prevention of non-melanoma skin cancer in organ transplant patients by regular use of a sunscreen: a 24 months, prospective, case–control study

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Summary

Background Skin cancers represent a major challenge within the ever growing group of long time surviving organ transplant recipients (OTR) world wide. Especially UV-induced non-melanoma skin cancers (NMSC) like invasive squamous cell carcinomas (SCC) and actinic keratoses (AK), and basal cell carcinoma (BCC), outnumber every other form of cancer in organ transplant recipients. Despite encouraging reports of protective effects of broad-spectrum sunscreens in immunocompetent patients, evidence for the prevention of NMSC in immunocompromised patients is still missing.

Objectives To assess preventive effects of regular sun-screen use on AK, SCC and BCC in chronically immunocompromised organ transplant recipients.

Methods Hundred and twenty matched (age, sex, skin type, graft, transplant duration, previous post-transplant skin malignancies) organ transplant recipients (40 heart, 40 kidney, 40 liver grafted) were recruited for this prospective, single-center study. Both groups received equally written and oral information on sun protection measures. Sixty patients were provided with a free broad spectrum study-sunscreen (SPF > 50, high-UVA absorption) for daily application of 2 mg cm^{-2} to the head, neck, forearms, and hands.

Results All 120 patients completed the 24 months study. Within this 24 month study interval 42 of the 120 patients developed 82 new AK (−102 sun screen group vs. + 82 control; $P < 0{\cdot}01$), 8 new invasive SCC (0 vs. 8; $P < 0{\cdot}01$) and 11 BCC (2 vs. 9; ns). In spite of equal numbers of AK at baseline, a marked difference in favor of the intent-to-treat sunscreen group was recorded after 24 months (89 vs. 273; $P < 0{\cdot}01$, mean difference 3·07 [1·76–4·36]) and the lesion count was significantly lower as compared to the initial visit (89 vs. 191; $P < 0{\cdot}01$, mean difference 1·7 [0·68–2·72]). With an average of 5·6 applications per week throughout the 24 months the study sunscreen was generally well tolerated. Serum 25-hydroxy vitamin D levels as marker for vitamin D status were decreased in all patients without adequate substitution and 25(OH)D was found to be lower in the sunscreen-group as compared to the control group (mean value 53 ng mL^{-1} vs. 60 ng mL^{-1}).

Interpretation Regular use of sunscreens, as part of a consequent UV-protection strategy, may prevent the development of further AK and invasive SCC and, to a lesser degree, BCC in immune-compromised organ transplant recipients.

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Conflicts of interest
C. U. has acted as a paid consultant to Almirall, Spirig, Novartis, Wyeth and has received funding for research carried out in his work. J.S.J. has received funding for research by Wyeth. M.U. has acted as a lecturer for Mavig GmbH, Almirall GmbH and Spirig GmbH. The author was awarded a research grant by MEDA Pharma GmbH in 2008. J.E. has acted as a paid consultant to Roche Diagnostics. W.S. has acted as a paid consultant to Abbott, Almirall, Janssen-Cilag, Novartis, Intendis, Schering-Plough, Serono and Wyeth. E.S.has acted as a paid consultant to Meda, Mavig, Almirall, Spirig, Heidelberg Pharma, Intendis and has received funding for research carried out in his work. The remaining authors declare no conflicts of interest.

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Organ transplant recipients (OTR) are highly susceptible to developing non-melanoma skin cancer (NMSC) such as actinic keratoses (AK), invasive squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Due to their aggressive features and their multiplicity in some individuals NMSC meanwhile represent one of the key challenges in the long term care of

this growing patient group. The risk factors for the development of NMSC in OTRs include duration and intensity of immunosuppression, age, lighter skin type, and male gender. Whereas in temperate climates between 35% and 50% of OTR will develop one or more skin cancers by the tenth year following organ transplantation[1] this number may rise to more than 80% in countries with a higher ultraviolet radiation (UV)-index such as Australia.[2] For long times the prevention of NMSC had low priority in the pre-transplant and early post-transplant period.[3] Since the average post-transplant survival time is steadily increasing, the NMSC incidence will continue to accelerate and hence require careful evaluation of primary and secondary prophylaxis in this group.[4,5]

In immunosuppressed as well as in immunocompetent populations, AK and SCC, but also BCC, are mainly localized on sun-exposed areas (face, neck, trunk, hands).[6,7] Highlighting the crucial impact of UVR on the development of NMSC, even in OTR the non-UVR exposed skin stays remarkably clear from NMSC.

While initiating and promoting NMSC, ultraviolet radiation (UVR) has a well-established role as a complete carcinogen.[8] Although childhood and adolescent UVR exposure have been identified as key factors for the induction of malignant melanoma and, to a lesser degree NMSC, the incidence of SCC increases with age and is causally related to the cumulative as well as recent UVR-exposure.[9,10] Against a background of systemically impaired immunosurveillance, the cumulative exposure to UVR represents the dominant risk factor for NMSC in OTR.[11,12]

Resolute use of sunscreen has been shown to reduce the incidence of AK[13,14] and cutaneous invasive SCC[15] in immunocompetent subjects.

Consequently, in OTRs all primary prevention measures have emphasised the importance of daily sunscreen use as part of the UVR-protection measures (Table 1).

Multiple studies have shown poor compliance rates regarding consequent sun protection among OTR.[3,16–18] Reasons given for not using sunscreens are manifold. They reach from lack of knowledge regarding the harmful effects of UVR, financial inability to afford high-quality sunscreens, to finding sunscreens too expensive, cosmetically unacceptable (greasy, comedogenic, difficult to rub in) or impractical in the social environment (whitening effect). Potentially most important is the fact that immunosuppressant drugs, especially calcineurine inhibitors, mTOR-inhibitors and corticosteroids induce sebaceous gland hyperplasia, folliculitis, acne, and a socially disturbing whitening effect. Such factors undermine the motivation of the OTR towards using sunscreens.

In this study, we examined the effect of the regular use of sunscreen on the incidence of new actinic keratoses, invasive squamous cell carcinoma and basal cell carcinoma in organ transplant recipients presenting during 24 months.

Table 1 Photoprotection advised for organ transplant recipients

Avoidance of sun exposure between 00:11 and 14:00 h
Strict avoidance of UV light from artificial sources (sun beds)
Daily application of sun screen cream [SPF 50 + including high-level UVA-protection (Australian Standard)]
Sun-impermeable clothes and head gear (broad brimmed hat favourable over cap)

Materials and methods

Approval for the study was obtained from the ethics committee of the Charité Universitätsmedizin, Berlin, and the study was conducted in compliance with current US and EU regulations.

Study objectives

The *primary objective* of this consecutive study was to compare regular and application of a highly protective sunscreen versus reinforced but self-responsible translated sun-protection with respect to prevention of AK, invasive SCC and BCC.

Three outcome variables were identified for the study: the total number of AK in the study area (head, neck, dorsum of the hands and forearms). The number of new AK lesions appearing or disappearing during the study, and the incidence of new invasive SCC and BCC during the study period.

A *secondary objective* was to compare skin infections (HPV-induced vulgar warts, herpes virus simplex, dermatomycoses) and acneiforme skin conditions as a result of chronic application of sunscreen lotion.

Incidences of skin infections (herpes simplex, vulgar warts, dermatomycoses, folliculitis) and potential side effects (i.e. acne, allergic reactions) of chronic application of the study sunscreen were recorded.

Participants

Twenty heart, 20 kidney and 20 liver transplant recipients, male or female (matched 1 : 1), who at the time of initiation were older than 40 years [median 60·7 years (40–77)] were randomly chosen from a collective regularly presenting to our specialised OTR skin clinic at the Charité University Hospital in Berlin, Germany (Table 2) and were recruited as the sunscreen group. To ensure equally matched risk factors in both study arms, 6 patients of each organ specific sub-group have

Table 2 Demographic summary of study participants

	Group	
Measurement	Control	Sun screen
N	60	60
Mean (± SD)		
Age, years	60·7	60·5
Age range, years	40–77	40–77
Male, %	50	50

been transplanted <1 year ago, 7 received their transplant between 1 and 5 years prior of entering the study and 7 patients were 7 or more years post transplant. Males and females of each subgroup were equally matched. All patients had Fitzpatrick's skintype II or III. An equally sized and matched group (age, sex, time post transplantation, grafted organ, previous posttransplant malignancies including similar numbers of AK) was identified from our database and recruited as the control group (Table 3). Inclusion and exclusion criteria are shown in Table 4.

The type of immunosuppression was comparable in the sunscreen and control arms of all three groups and consisted of cyclosporine, mycophenolate or azathioprine and prednisolone in the heart transplant group, tacrolimus, mycophenolate and prednisolone in the kidney group, and a tacrolimus based regimen in the liver transplant group. All patients remained on their type of immunosuppression during the whole 24 months of observation. Dose adjustments, if at all, were not related to the occurrence of NMSC but mainly related to medical needs such as graft function.

Table 3 Summary statistics at enrolment

	Group	
Measurement at enrolment	Control	Sun screen
Initial actinic keratoses	191	191
Mean (± SD)	3·23 (3·659371)	3·18 (3·42)
Range	0–12	0–11
Prior invasive SCC	6	7
Prior invasive BCC	6	6

Sunscreen

The study sunscreen was a water resistant cream lotion containing the filters bis-ethylhexyloxyphenol methoxyphenyl triazine, ethylhexyl triazone, isoamyl p-methoxycinnamate, ethylhexyl methoxycinnamate and methylene bis-benzotriazolyl tetramethylbutylphenol, butyl methoxydibenzoylmethane (Daylong actinica®; Spirig Pharma Ltd., Egerkingen, Switzerland). It is rated as 'very high protective' according to the EU commission recommendation (26/9/2006) notified under document number C(2006)4089. The labeled category 'very high protective' corresponds to a measured sun-protection-factor (SPF) > 60 for UV-B. According to the Australian Standards (AS/NZS 2604–1997) the product delivers a good UV-A protection.

Study procedures

After individual informed consent patients were examined and interviewed regarding previous skin diseases and especially NMSC. Lesions in the study areas (head, neck arms back of the hands, and lower forearm), clinically identified as AK were counted. Biopsies were taken out of any hyperkeratotic AK (AK III) or lesions with clinical suspect of invasiveness (SCC, BCC). All confirmed AKIII, invasive SCC and BCC were surgically removed. Any lesion treated during the course of the study was rated positive till the end of the 24 months observational phase.

Patients in the sunscreen and in the control group received the same oral and written information on sun-related skin cancers and sun-protection measures, including the use of sunscreen. They were advised to keep out of the sun from 11:00 to 14:00 h, wear UVR-proof hats or caps and long

Table 4 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Patients of either sex aged ≥ 40 years	Invasive or immediate pre-invasive (AK III) skin tumours at time of study inclusion
Organ-transplant recipients who received a liver, kidney or heart transplant	Multi-organ transplantation
Patients or legal representatives who are able to understand and provide written informed consent to participate in the clinical investigation (signed informed consent)	Evidence of systemic infection, excluding viral hepatitis, at the time of recruitment
	Evidence of chronic transplant dysfunction
	Known or supposed systemic malignant tumour or systemic chemotherapy within the last 5 years prior randomisation
	Patients participating in a clinical trial within the last 4 weeks before study
	Patients treated with the antitumour/antiangiogenetic immunosuppressant sirolimus, respectively everolimus at the time of randomisation
	Patients treated with sirolimus/everolimus or any other medication associated with reduced tumour incidence at Screening
	Planned or past change of immunosuppression < 3 months ago
	Present or planned interferon therapy (in liver transplant patients with hepatitis B/C)

sleeved shirts and trousers (Table 1). In the sunscreen group all patients were provided with unlimited free sunscreen during the entire observation period and were advised and trained to apply 2 mg cm^{-2} lotion on the face and neck and back of their hands, and lower forearm as well as other sun-exposed parts of their skin 20–30 minutes before leaving the house for the first time of the day. At each visit patients of both groups were interviewed about their sun protective behavior including the frequency of sunscreen use, textile UV-protection and outdoor behavior. Patients of the sunscreen group also documented this data in a diary. All patients presented every 6 months (March–April and September–October) for their clinical evaluation and interview and disposal of new doses of study sunscreen for the intend-to-treat arm. The examinations were done by a team of three experienced dermatologists. In case of occurrence of new skin lesions the patient presented at unscheduled visits.

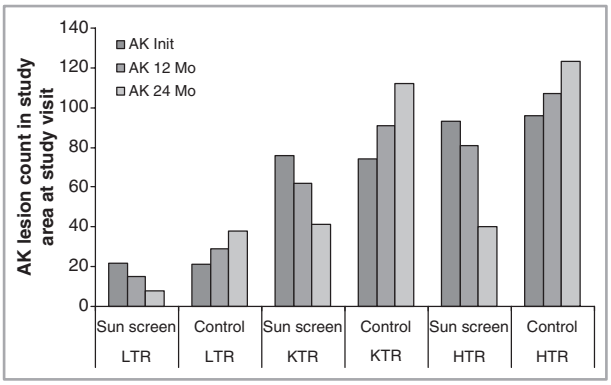

Fig 1. Actinic keratosis (AK) lesion counts before, at 12 and 24 months (LTR, liver transplant recipient; KTR, kidney transplant recipient; HTR, heart transplant recipient).

Statistical analysis

Continuous data were compared by the t-test and ANOVA in SPSS 14.0 (SPSS GmbH Software, München, Germany). If distributional assumptions were in doubt nonparametric test were used. Categorical values were compared with Fisher's exact test. A P-value of $< 0{\cdot}05$ was considered significant.

Results

Actinic keratoses

All patients completed the 24 months study phase. Within the 24 month study interval 42 of the 120 patients developed 82 new AK and 102 AK (all in the sunscreen group) went into spontaneous remission. The lesion count was significantly lower (−102 sun-screen group vs. plus 82 control; $P < 0{\cdot}01$, mean difference 3·07 [2·47–3·65]). 3 of the 60 patients in the sunscreen group had up to two additional (and newly developed) AK at the 12 months visit, but these lesions regressed within the following 12 months until the final visit without specific therapy applied. Altogether the incidence of new AK after 24 months was significantly lower in the intent-to-treat sunscreen group as compared to the control group (89 vs. 273; $P < 0{\cdot}01$, mean difference 3·07 [1·76–4·36]) and significantly lower as compared to the lesion count recorded in the initial visit (89 vs. 191; $P < 0{\cdot}01$, mean difference 1·7[0·68–2·72]) (Fig. 1). In the sunscreen group an overall reduction of 53% in AK numbers as compared to initiation visit was observed after 24 months. In the control group the AK numbers overall increased by 43%.

The highest numbers of AK were found in the highly immunocompromised heart transplant group (189 lesions at the pre study visit), followed by kidney (150) and liver (43) transplant recipients. However, there was a remarkable decrease of AK in sunscreen groups of all three transplant populations. In the heart transplant recipients sun-screen-group the numbers decreased form 93 lesions pre study to 81 at 12 months (13% reduction, mean difference 0·6, P [ns]) to 40 after 24 months of resolute sunscreen use (56% reduction, mean difference as compared to baseline 2·65, $P = 0{\cdot}03$). Similar effects were observed in the sun-screen groups of the kidney [76 AK pre visit, 62 (18% reduction) after 12 months, 41 (46%) after 24 months; P = ns] and liver transplant recipients [22 pre visit, 15 (32%) after 12 months, 8 (64% reduction) after 24 months] ($P = 0$, 1 [ns]).

In the control group; however, the numbers of AK steadily rose throughout the study, reaching an increase of 28% (96 AK pre study, 123 AK at 24 months) in the heart transplant group after 24 months. In the kidney transplant group the AK numbers in the defined study area increased by 51% (74 AK pre study, 112 AK post study) and in the liver grafted control group by 81% (21 AK pre study vs. 38 post study).

Squamous cell carcinoma and basal cell carcinoma

Twenty five out of the 120 patients taking part in this study had invasive NMSC (Table 3) in their post transplant history before entering the study (13 BCC, 12 SCC). 19 new invasive NMSC (BCC, SCC) were found in 22 patients during the 24 months study phase. In the sun-screen group no new invasive SCC occurred whereas in the control group patients developed eight new invasive SCC (5 in heart transplanted patients, 3 in kidney and none in liver transplant recipients) (0 vs. 8; $P < 0{\cdot}01$) (Fig. 2).

In contrast to the highly significant difference in the proportion of patients with newly developed SCC the incidence of BCC was less striking. The sun-screen group patients developed 2 new BCC whereas in the control group the patients developed 9 new BCC (2 vs. 9; P = ns) (Fig. 3). one of the new BCC in the sun-screen-group developed in liver and one in a kidney transplant recipients. In the control group 3 new BCC were found in liver, 4 in kidney and 2 in heart transplant recipients. All SCC and BCC were clinically diagnosed, excised and histological confirmed.

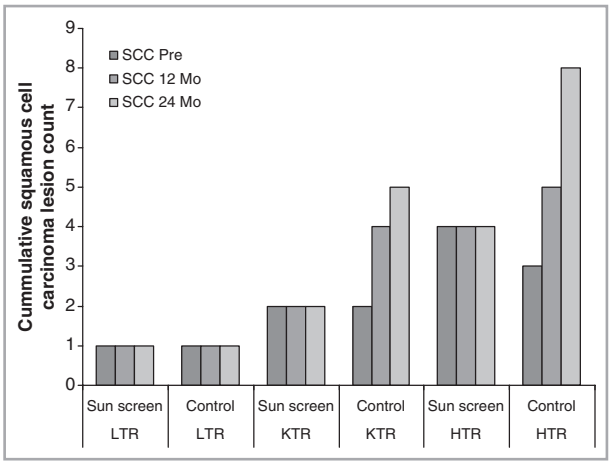

Fig 2. Cumulative incidence of squamous cell carinoma (SCC) before, at 12 and 24 months.

Adverse effects

In both groups (sunscreen and control) acne or increased seborrhea as potential side effects of application of sun screens (study sun screen or individually purchased sun screen) was reported. Twelve out of 60 patients in the sunscreen group occasionally complained about seborrhea and acne, which was usually very variable throughout the study and mostly manageable with increased cleansing of the facial skin in the evening. Acne (two patients) and seborrhea of the face was also reported in 7 out of 60 patients in the control group, showing the usual side effects of calcineurin inhibitors and corticosteroids in OTR. In the sunscreen group, there was a non-significant trend towards less human papilloma virus induced warts on the dorsum of the hands and lower arms. However, since a proportion of warts also occurred on palmar and plantar soles or other not typically sun-exposed areas of the skin, they were not analysed in a more detailed way within this study. There was no difference between the groups in connection with further infectious skin diseases including herpes simplex, herpes zoster or dermatomycoses.

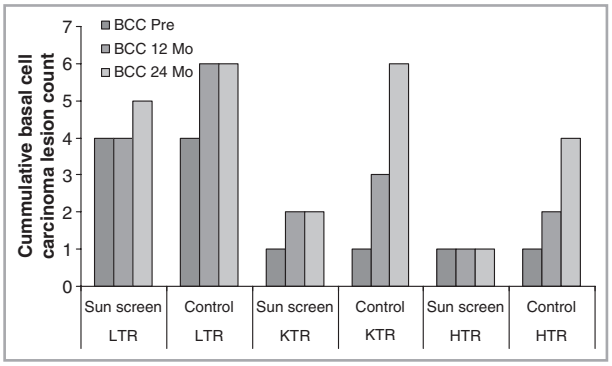

Fig 3. Cumulative incidence of basal cell carcinoma (BCC) before, at 12 and 24 months after daily application of 2 mg cm^{-2} sunscreen product to sun exposed study areas.

Discussion

UV radiation is the major environmental cause for non-melanoma skin cancer. An increased cumulative lifetime dose of sun exposure is associated with the increased risk of AK and invasive SCC.[5,19] AK were previously described as serving as a 'dosimeter' for the life time sun-exposure and representing a major risk factor for subsequent skin cancer.[1,10,14,18] Organ transplant recipients have particularly high rates of actinic keratoses and squamous cell carcinoma with a relative risk ~ 100- fold higher than that in the immunocompetent population.[19] 93·5% of all squamous cell carcinomas occur in the typical 'sunny terraces' of the body, mainly head, neck, dorsum of the hands and forearms.[3] Whereas in immunocompetent patients, only ~ 10% of individual lesions of actinic keratosis advance to invasive squamous cell carcinoma during a 5- to 10-year time frame, in OTR the rate of progression of actinic keratosis is apparently accelerated (months) and the incidence of progression higher (> 20–30%).[20]

Sunscreens can inhibit the formation of actinically induced neoplastic lesions. They are able to reduce the prevalence of actinic keratoses and recurrent SCC in immunocompetent patients.[13–15] Assuming the same in an setting of systemic immunosuppression, sun avoidance strategies including the recommendation of a daily use of sun screen is included in all guidelines for skin cancer prevention in OTR.[5,21]

Non-melanoma skin cancer

Up to our knowledge, this is the first study to document that regular application of sunscreen has a preventive impact on the development of NMSC in the high risk-group of organ transplant recipients. Whereas during the 24 month study interval 42 of the 120 patients developed new AK, the total number of AK at the 24 months visit decreased by 102 in the intend-to-treat sun screen group. The control group, equally informed about the importance and applicable techniques of sun protection measures, however, showed a significant increase of 82 lesions in the same time ($P < 0{\cdot}01$). It has been reported in the past that AK may spontaneously remit if sunlight exposure is reduced.[22] Even transplant patients often presented with lesions whose onset or worsening was noticed during the summer, suggesting that the lesions may become more active following sunlight exposure. Studies examining the effect of UVR mediated alteration of the epidermal immune surveillance mediated by Langerhans cells could partly explain this seasonal variation.[23] These findings may indicate remaining capacities of the cutaneous immune surveillance in the clearance of early forms of epithelial dysplasia in the absence of UVR even in OTR.

The rationale for treating and preventing AK is to prevent progression to invasive SCC. In our study, eight new invasive SCC developed in the control group whereas patients in the sunscreen group remained free of new SCC. Though the overall incidence rates were small, these findings were statistically significant ($P < 0{\cdot}01$). They back up earlier results from the

Australian Nambour Skin Cancer Trial on 1383 immunocompetent subjects, showing a significantly lower incidence of SCC in the group with daily use of sun screen.[15]

Out of the 60 patients in the sun screen group 2 developed a new BCC during the time of the study. In the control arm we detected nine new BCC. Though, the results indicate a benefit in favor of the sunscreen group, the results where not statistically significant. Generally, basal cell carcinomas are 'only' increased by a factor of 10 in organ transplant recipients. A possible explanation for our findings could be, that infrequent intense exposure to UVR may have a greater impact on increasing the risk of BCC compared with the total cumulative UV exposure.[24] However, further studies or a longer follow-up is needed to elucidate a significant impact of sun protection and basal cell carcinoma dynamic.

Sunscreens

Sunscreens are topical preparations that attenuate the effects of UV radiation on the skin. The poor compliance among OTR with advised sun protection measures and especially sun screen use has been shown before.[16,17,25] When evaluating the reasons given by those patients denying regular sunscreen use despite the knowledge of the deleterious effects of UV radiation, two main groups of 'excuses' usually arise. The largest group describes sunscreens as 'cosmetically and socially unacceptable'. Indeed, the physical inorganic filters (titanium or zinc oxide), which are the protective compounds in some broad-spectrum sunscreens recommended to organ transplant recipients, have a more greasy 'feel'.[26,27] They are difficult to apply and are not recommendable for oily skin or for skin with acne. The latter aspect might be even especially important for OTR since cyclosporine induces sebaceous gland hyperplasia, leading to a seborrhoic skin and acne. Steroids, and also newer immunosuppressive agents such as everolimus and sirolimus (mTOR-inhibitors), are also able to induce or promote acne. Patients therefore usually try to avoid or reduce application of any additional fatty emollients to their face which frequently also includes sunscreens. Optimized formulations for these patients, such as gels or liposomal lotions, are less greasy and likely to be more cosmetically acceptable. With an average of 5·6 application out of 7 application days per week, the acceptance and compliance with our liposomal study sunscreen lotion was excellent. Since only a correctly applied sunscreen has a chance to protect the individual, cosmetic preference of a patient plays a frequently underestimate role.

The second reason given for non-complying with the advised use of sunscreen, are the costs of high quality sun screens. Many of our patients had to retire early due to their transplant or the prolonged time on the transplant-waiting list and are not doing too well financially. Health insurance companies still consider all sunscreens to be 'cosmetic' products. Consequently, they are not reimbursed even for patients at high risk of skin cancer, such as organ transplant recipients. Interestingly, a recent study proofs regular sun screen use as a cost–effective approach to skin cancer prevention in a subtropical setting, which may serve as a calculational example for other NMSC risk-groups too.[28] Protective measures with textiles, hats and sun avoidance are primary precautions for OTR. Since sun screens are recommended for those parts of the body which are not sufficiently protected by textiles, the daily costs originating from sun screen use are therefore limited.

With an average of 5·6 out of 7 applications per week year round for a total of 24 months in the sunscreen group, the compliance and acceptance of the study sunscreen was excellent. Patients in the control group typically applied sunscreen if directly exposed to UVR, mostly related to recreational activities in summer months. The year round average sunscreen application frequency in the control group was less than once per week (0·3 days). Furthermore (97%) of the sunscreen- and (84%) of the control group patients reported to trying to keep out of the midday sun on a sunny day.

Vitamin D

Sun protection can decrease pre-vitamin D3 synthesis in skin and the question about the importance of optimal vitamin D levels for general health is currently a hot topic both in popular press and in the scientific literature and is discussed by Reichrath *et al.* in another article of this supplement. On the other hand, excessive sun exposure may also have unwanted side effects on vitamin D metabolism: vitamin D synthesis is maximal at suberythemal UV doses and further UV exposure only increases the conversion of pre-vitamin D3 to lumisterol and tachysterol, both biologically inert compounds.[29] Furthermore, continued sun exposure degrades the active form of the photolabile vitamin D3.[30] In our study, vitamin D levels were not measured prospectively in all patients. However, at 24 months, patient-data of the past 30 months was collected from transplant centres and values measured from frozen serum samples were used to amend missing data in some patients. Serum 25(OH)D levels, as marker for vitamin D status, were decreased in the obtainable values of patients without adequate substitution (normal range: 15·0–90·0 ng mL^{-1}). With mean values from 53 ng mL^{-1} in the sunscreen and 60 ng mL^{-1} in the control group, we were not able to reconfirm lower levels of 10·9 ng mL^{-1} 25(OH)D associated with rigorous sun protection in 31 renal transplant recipients in a recent publication.[31] Anyhow, we would strongly advise to interdisciplinary monitor Vitamin D levels of all patients with regular sun protection and especially OTR. If not already performed by the transplant-internists, dermatologists should advise oral substitution of vitamin D deficiency as previously described.[29,32]

Conclusion

Skin cancer remains a significant challenge for dermatologists in the management of organ transplant recipients. However, the accelerated skin carcinogenesis seen in this particular group of immunocompromised patients makes them an ideal

population in which to study the potential of preventive and therapeutic measures. Sunscreens, as part of a conclusive sun protection strategy, are an important pillar of preventive healthcare. Our findings lend support to the hypothesis that intensified use of cosmetically acceptable, highly protective sun screens in combination with educational programs and behavioural changes may reduce the increased risk for developing distinct forms of non-melanoma skin cancers in a NMSC-high-risk patient population. We conclude that for all individuals with an increased risk of skin cancer development sun protective measures including highly protective sunscreen must be employed throughout their life.

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