

CLINICAL REPORT

Sun Habits in Kidney Transplant Recipients with Skin Cancer: A Case-control Study of Possible Causative Factors

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Organ transplant recipients are frequently affected by skin cancer, which might also be a major cause of long-term mortality. Excessive sun exposure is considered to be a factor in the aetiology, but uncertainty about the importance of this and other proposed risk factors remains. The purpose of this study was to investigate sun behaviour before and/or after the transplantation in kidney transplant recipients with or without cutaneous squamous cell carcinoma. A nested, population-based, case-control study was carried out on 95 kidney transplant recipients who had contracted cutaneous squamous cell carcinoma after the transplantation and on an accurately matched control population of 154 kidney transplanted patients. Information on sun exposure before and after the transplantation, skin type, use of sunbeds, warts, etc., was obtained from a questionnaire which contained 38 detailed questions. The differences between cases and control subjects were not significant for sun exposure before or after the transplantation, sun protective measures, number of sunburns, outdoor occupation, smoking habits or use of sunbeds. Compared to patients with skin type IV, the cutaneous squamous cell carcinoma odds ratio was 3.0 (95% CI = 1.3–7.0) for skin type I+II. Patients with light blond or red hair colour also had a higher odds ratio than those with dark hair, 3.2 (95% CI = 1.2–8.2), and patients with warts after the transplantation had a higher odds ratio than those without, 2.2 (95% CI = 1.2–4.2). In conclusion, poor tanning ability rather than the amount of sun exposure is associated with the development of cutaneous squamous cell carcinoma in kidney transplant recipients and warts appearing after the transplantation indicate increased risk. **Key words:** case-control; epidemiology; kidney transplant; squamous cell carcinoma; sun behaviour.

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Skin cancer is the most common malignancy affecting organ transplant recipients (1–10). For cutaneous

squamous cell carcinoma (CSCC) there is a 100-fold increased risk (10). Significant increased risks of cancer in other organs have also been reported (11, 12). The risk factors for skin cancer may differ in this population compared to the immunocompetent normal population. The major contributing factors for the carcinogenesis are considered to be ultraviolet radiation (UVR), drug-induced immunosuppression and human papillomavirus infection (HPV) (3, 13–15). Moreover, skin cancer in kidney transplant recipients (KTRs) might be associated with a higher risk of metastasis than skin cancer in the general population (3, 16). As expected, the rate of skin cancer in KTRs in Australia is high, probably because of the high sun exposure (7), and a recent study has shown that skin cancer is a cause of morbidity and long-term mortality in heart transplant recipients (9). In Sweden, too, with much less sun exposure, the risk of CSCC is very much increased following solid organ transplantation (10). Against the background of these studies, and in view of the uncertainty about the contribution to the aetiology of skin cancer from sun exposure before and/or after the transplantation, skin type and other factors related to life-style, we carried out this nested, population-based, matched case-control study on KTRs.

PATIENTS AND METHODS

Study population

The Swedish organ transplant cohort, described in detail elsewhere (10) and at present comprising 6457 patients who underwent organ transplantation between 1970 and 1997, formed the basis of the study. This cohort comes from the Swedish In-patient Register and has been linked with the Swedish Cancer Register in order to identify all cancer cases among the transplant recipients. After excluding unknown transplantation codes ($n=258$) or mismatching transplantation dates ($n=12$), 5004 KTRs remained. In this cohort, 267 patients had CSCC.

At the beginning of the observation period, patients received immunosuppression mainly with azathioprine and prednisone, but since the introduction of cyclosporine in 1983 most patients have received this drug in combination with the other two.

The study area was Sweden (55° N–69° N), where annual residential sunlight exposure is between 1300 and 2000 MED UV radiation.

Table I. Summary of questionnaire for kidney transplant recipients with or without cutaneous squamous cell carcinoma

Item	No. of questions
Lifetime sun exposure through work and leisure. Use of sunbeds	5
Attitudes to sunbathing	6
Sun protection measures. Creams and clothes	8
Given advice on reducing sun exposure and on skin cancer. From whom?	4
Skin type, hair and eye colour, smoking habits and occupation	10
Kidney disease, transplantation and immunosuppression	2
Skin diseases	3
Total	38

For 18 questions, answers were divided into 3 different time periods: before kidney disease, during dialysis and after transplantation.

Study design

We selected the 124 living KTRs from the study population who had CSCC after the transplantation. For each cancer case, living control patients cancer-free at the time of cancer diagnosis for the case were selected from the study population on the basis of age and year of transplantation ± 5 years. This procedure resulted in 178 control patients.

A detailed questionnaire (summarized in Table I) was mailed to 302 patients. After one reminder, 251 patients had answered (83%). Ninety-five cancer cases and 154 controls were evaluated. Fifty-nine cases had 2 controls and 36 had one (Table II). All patients were Caucasian and they were classified by skin type I–IV according to Fitzpatrick (17). We assumed that non-responders to the question about warts before (14.9%) and after (8.4%) the transplantation had no warts, and that non-responders to the question about outdoor occupation (4%) had no outdoor occupation. A relatively high non-response rate was noted for sunscreen (6%), skin type (5.6%) and outdoor tanning before kidney disease (4%). For the other questions, the non-response rate was 1–3%.

Statistics

The methods of analysis were those described by Breslow & Day (18) for matched case-control studies. Odds ratios (OR) were calculated by conditional maximum likelihood estimation and are presented with their associated 95% confidence intervals (CI). Conditional logistic regression analysis was performed with the SPSS software package (SPSS Advanced Statistics 10.1 Chicago: SPSS Inc; 2001).

Table II. Characteristics of the two groups of patients

	Cancer patients	Controls patients
Total number	95	154
Sex, M/F		
<i>n</i>	61/34	89/65
%	64/36	58/42
Age at transplantation		
Mean	45	45
Range	12–70	14–70
Duration of transplant at investigation (years)		
Mean	16	16
Range	6–30	5–29
Duration of dialysis before transplantation (years)		
Mean	1.5	1.6
Range	0–13	0–18

RESULTS

Fig. 1 illustrates the sun behaviour of the patients before transplantation, during dialysis and after transplantation. The changes among the cases and controls showed no statistically significant differences between tanning behaviour before and after the transplantation.

Compared to patients with skin type IV, CSCC OR was 3.0 (95% CI = 1.3–7.0) for skin type I+II. Patients with light blond or red hair colour also had higher OR than those with dark hair: 3.2 (95% CI = 1.2–8.2) (Table III) and patients with warts after the transplantation had higher OR than those without: 2.2 (95% CI = 1.2–4.2) (Table IV). In a multivariate model with both skin type and hair colour, only hair colour remained significant ($p = 0.04$) and was therefore selected to represent sun sensitivity (see Table IV).

No relationship was observed between CSCC and sex, sunscreen use, number of sunburns, use of sunbeds, outdoor occupation, warts before transplantation, eye colour or smoking habits. Compared to patients with brown eyes, patients with other colours (blue, grey, green, mixed) had a univariate OR of the same magnitude as patients with skin type I+II or patients

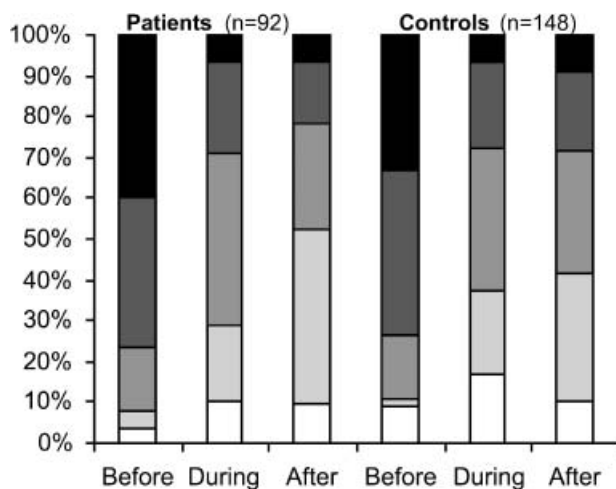


Fig. 1. Sun behaviour before and after transplantation and during dialysis of kidney transplant recipients with ("Patients") and without ("Controls") cutaneous squamous cell carcinoma post transplantation. □ Have never sunbathed; ■ Have stopped sunbathing; ■ Seldom in the sun; ■ Sometimes in the sun; ■ Often in the sun.

Table III. Relationship of cutaneous squamous cell carcinoma to skin type and hair colour

	No. of patients (%)	No. of controls (%)	OR	95% CI	OR*	95% CI
Skin type						
IV	21 (23)	52 (37)	1.0		1.0	
III	45 (49)	67 (47)	1.9	0.9–3.7	2.2	1.0–4.8
I+II	26 (28)	24 (16)	3.0	1.3–7.0	4.0	1.5–11.0
Total	92 (100)	143 (100)				
Hair colour						
Dark	27 (29)	55 (37)	1.0		1.0	
Blond	51 (55)	83 (55)	1.3	0.7–2.4	1.6	0.8–3.2
Light blond/red	15 (16)	13 (8)	3.2	1.2–8.2	5.0	1.5–16.7
Total	93 (100)	151 (100)				

*Adjusted for sex, sun exposure before transplantation, outdoor occupation.

Table IV. Relationship of cutaneous cell carcinoma to common warts of the patients

Time period	No. of patients (%)	No. of controls (%)	OR	95% CI	OR*	95% CI
Warts before transplantation:						
No	60 (63)	97 (64)	1.0		1.0	
Yes	35 (37)	54 (36)	1.0	0.6–1.7	1.2	0.6–2.2
Warts after transplantation:						
No	21 (22)	58 (38)	1.0		1.0	
Yes	73 (78)	96 (62)	2.2	1.2–4.2	2.3	1.1–4.9

*Adjusted for sex, sun exposure before transplantation, hair colour, outdoor occupation.

with light blond or red hair (OR = 3.3) However, this was not significant (95% CI = 0.7–15.2)

Forty-two percent of cases and 39% of controls had received advice about sun protection in connection with the transplantation.

DISCUSSION

There is ample evidence and general agreement that excessive exposure to sunlight, by altering DNA, is the most important environmental cause of skin cancer in man. Further, the specialized cutaneous immune system, which is important in the repair of such damage, is suppressed by UVR, and this suppression is 2- to 3-fold greater in subjects with skin types I/II than in those with skin types III/IV (19). It is therefore not surprising that systemically immunosuppressed KTRs develop skin cancer on sun-exposed areas (1–14). Patients can influence their exposure to sunlight after advice in connection with the transplantation, but previous exposure is unaffected. The relevance of sun behaviour before and after transplantation to the risks of developing a CSCC was therefore analysed. We also analysed some possible non-solar risk factors.

The sun behaviour of patients before and/or after the transplantation did not differ significantly between cancer cases and controls with regard to the amount of sun exposure, number of sunburns, protective measures, number of vacations at sunny resorts or outdoor occupation. These findings were surprising and suggest

that other factors, such as sun sensitivity, are more important for determining skin cancer risk and that much of this carcinogenic risk was already acquired pre-dialysis/transplantation, since a significant change in behaviour, as shown in Fig. 1, is not obviously related to a reduction in skin cancer risk. A certain amount of recall bias may affect the study, but the answers to questions with little possibility of bias, e.g. outdoor occupation, were in line with the overall findings. Although this study contained all the living KTRs in Sweden with CSCC its power was limited and the results must therefore be interpreted with caution. The most important finding was an increased risk of CSCC in patients with poor tanning ability (skin types I and II) and other pigmentary traits typical of a low level of natural protection against the sun (light blond hair). This finding is consistent with an earlier study of KTRs (21), where 51% of the patients with non-melanoma skin cancer had skin type I or II. In a recent study of heart transplant recipients in Italy, skin type II and also sunlight exposure > 10 000 h were significant risk factors for skin cancer (21). In our study, we could only confirm the increased risk for patients with skin types I and II and not for excessive sun exposure. The cumulative sun exposure of the KTRs (also included) in the Italian study, however, differed significantly from that of our KTRs. The median accumulated sun exposure in the Italian KTRs without skin cancer was 0 h, while median age was 44.5 years compared to 27 years in the control group.

Cases and controls had changed their sun behaviour after the transplantation, but also during dialysis (Fig. 1). The decreased sun exposure during dialysis might be explained by the fact that the patients were severely affected by kidney disease and the time-consuming dialysis. After dialysis, however, the patients continue to have lower sun exposure than before the disease period. This could be explained partly by the fact that older patients probably spend less time sunbathing and partly by the advice about sun protection received in connection with the transplantation. In a U.K. study, 54% of the KTR remembered being given such advice (22), and in our study only 42% of cases and 39% of controls stated that they had received such information. Thus the reason for the decreased sun exposure after the transplantation seems to be increasing age or general health rather than advice received.

Tobacco smoking is a risk factor for several cancers, including CSCC (23), and five questions about smoking habits were included in our questionnaire. However, we found no such association.

The HPV genus contains causative agents of cervical cancer, anogenital epithelial cancers and common warts (24). Several HPV types have been found in skin tumours from renal transplant recipients (25, 26), but are also common in normal skin of KTRs (27). We noted an increased risk of CSCC in patients with warts appearing after the transplantation. Warts are probably an indicator of the grade and duration of the immunosuppression and represent a heavy virus infection of the skin. The patients are systemically immunosuppressed and, further, locally immunosuppressed on sun-exposed areas. At the same time, the UVR causes DNA damage in skin that is HPV-infected. We believe that the coincidence of these factors is the most important element in the carcinogenesis of CSCC in KTRs. Recently, it has been shown that HPVs can block the epidermal apoptotic response to UV damage (28).

The use of sunscreens is usually low or inappropriate among KTRs (22, 29). Confusion and lack of knowledge may account for this, but cost may also be important, as sunscreens are expensive. However, suppression of the immune system of the skin by UVR can be prevented by a high-factor (SPF 29) sun-blocker (30).

In conclusion, most kidney transplant recipients decreased their sun exposure considerably during dialysis and post-transplantation; but this change in tanning behaviour, or their reported lifetime ultraviolet radiation exposure, did not affect the risk of CSCC significantly. However, poor tanning ability was associated with increased risk of CSCC, and factors associated with life-style, i.e. sun exposure, do seem to be less important than individual genetics, i.e. pigmentary traits. We conclude that patients with skin types I and II must be strictly advised to avoid sun exposure and patients with skin types III and IV

should receive advice on the risk of skin cancer and the need to take extra precautions against sun exposure. Moreover, patients with warts appearing after the transplantation should be followed more closely, as these seem to be an indicator of an increased risk of CSCC.

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