Prevalence of Skin Cancer and Related Skin Tumors in High-Risk Kidney and Liver Transplant Recipients in Queensland, Australia

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The increased skin cancer incidence in organ transplant recipients is well-known, but the skin cancer burden at any one time is unknown. Our objective was to estimate the period prevalence of untreated skin malignancy and actinic keratoses in high-risk kidney and liver transplant recipients and to assess associated factors. Organ transplant recipients underwent full skin examinations by dermatologically trained physicians. The proportion of examined organ transplant recipients with histopathologically confirmed skin cancer in the 3-month baseline period was estimated. Prevalence ratios with 95% confidence intervals indicated significant associations. Of 495 high-risk organ transplant recipients (average age = 54 years, time immunosuppressed = 8.9 years), 135 (27%) had basal cell carcinoma, squamous cell carcinoma or Bowen's disease (intraepidermal carcinoma) present and confirmed in the baseline period, with respective prevalence proportions of 10%, 11%, and 18% in kidney transplant recipients and 10%, 9%, and 13% in liver transplant recipients. Over 80% had actinic keratosis present, with approximately 30% having 5 or more actinic keratoses. Organ transplant recipients with the highest skin cancer burden were Australian born, were fair skinned (prevalence ratio = 1.61, 95% confidence interval = [1.07, 2.43]), reported past skin cancer (prevalence ratio =3.39, 95% confidence interval = [1.93, 5.95]), and were receiving the most frequent skin checks (prevalence ratio = 1.76, 95% confidence interval = [1.15, 2.70]). In conclusion, high-risk organ transplant recipients carry a substantial measurable skin cancer burden at any given time and require frequent review through easily accessible, specialized services.

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INTRODUCTION

Long-term immunosuppressive therapy greatly increases the incidence of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin among organ transplant recipients (OTRs) (Euvrard et al., 2003; Mackenzie et al., 2010; Zavos et al., 2011). As OTRs' long-term survival rates rise with advances in surgery and improved immunosuppressive drug regimens, so too does the burden of these keratinocyte cancers (Berg and Otley, 2002; Euvrard et al., 2003) and the associated health-care costs (Fransen et al., 2012; Ruegg et al., 2012).

To date, the cumulative incidence rates of skin cancer after organ transplantation have mostly been used to indicate OTRs' long-term skin cancer burden (Fortina et al., 2000; Haagsma et al., 2001; Martin et al., 2013; Ramsay et al., 2002). Period prevalence, the proportion of a population who have a disease present in a given time window, provides a measure of the net effects of incidence and treatment. To our knowledge, no prevalence estimates of skin cancer in OTRs are currently available, yet the outlay of necessary clinical services should be guided by this knowledge. We therefore assessed the period prevalence of skin cancers in a tightly defined window, as well as actinic keratosis (AK) baseline prevalence, in kidney and liver transplant recipients in Queensland, Australia. We assessed those at high risk of keratinocyte cancer because these are the OTRs who carry most of the skin cancer burden in a community. We also assessed risk factors associated with having keratinocyte cancer present on the skin in this period.

RESULTS

Of 735 kidney and 394 liver transplant patients at Princess Alexandra Hospital, 749 (kidney, n = 464; liver, n = 285) met

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Abbreviations: AK, actinic keratosis; BCC, basal cell carcinoma; OTR, organ transplant recipient; SCC, squamous cell carcinoma

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Table 1. Characteristics of 495 organ transplant recipients

Characteristics[1]	Kidney (n = 287)	Liver (n = 208)	*P*-value[2]
Age in years			
Overall, mean (SD)	54 (11)	55 (13)	
<40, n (%)	30 (10)	27 (13)	
40–49, n (%)	66 (23)	21 (10)	
50–59, n (%)	79 (28)	74 (36)	
60–69, n (%)	95 (33)	71 (34)	
70+, n (%)	17 (6)	15 (7)	0.001
Sex, n (%)			
Female	105 (37)	75 (36)	
Male	182 (63)	133 (64)	0.900
Born in Australia, n (%)			
No	55 (21)	47 (25)	
Yes	208 (79)	143 (75)	0.340
Natural complexion, n (%)			
Olive/medium	102 (36)	88 (44)	
Fair	182 (64)	113 (56)	0.080
Skin reaction to acute sun, n (%)			
Only tan	59 (23)	51 (27)	
Burn then tan	132 (50)	103 (54)	
Always burn	72 (27)	35 (19)	0.080
Presence of elastosis of neck, n (%)			
None	28 (10)	22 (11)	
Little	134 (47)	85 (43)	
Moderate	112 (39)	81 (40)	
High	11 (4)	13 (6)	0.500
Past skin cancers in last 2 years,[3] n (%)			
No	111 (42)	103 (54)	
Yes	152 (58)	87 (46)	0.010
Frequency of skin checks in last 5 years, n (%)			
Less than once a year	116 (44)	114 (60)	
Once a year	40 (15)	26 (14)	
More than once a year	107 (41)	50 (26)	0.002
Number of protection measures used for sun exposure, n (%)			
<2	120 (46)	97 (51)	
2+	143 (54)	93 (49)	0.250
Time (years) since first transplant[4]			
Overall, mean (SD)	11 (9)	9 (7)	
1–5, n (%)	90 (31)	71 (34)	
>5–10, n (%)	65 (23)	53 (25)	
>10–20, n (%)	88 (31)	68 (33)	
>20, n (%)	44 (15)	16 (8)	0.080
Immunosuppressive therapy regimens, n (%)			
Antimetabolites[5]	0 (0)	2 (1)	
Antimetabolites and calcineurin inhibitors	14 (5)	15 (7)	
Antimetabolites and corticosteroid	7 (2)	9 (4)	
Calcineurin inhibitors[6]	4 (1)	107 (51)	
Calcineurin inhibitors and corticosteroid	19 (7)	46 (22)	
Triple therapy[7]	240 (84)	25 (12)	
mTOR therapy[8]	0 (0)	2 (1)	
mTOR inhibitors and corsticosteroid	2 (1)	2 (1)	
Corticosteroid and anti-CD20 antibody[9]	1 (1)	0 (0)	

Abbreviation: mTOR, mechanistic target of rapamycin.
[1]Percentages do not add to 100% because of missing values.
[2]Chi-square *P*-value.
[3]Other than melanoma.
[4]Time in years since first transplantation was calculated based on date of first transplantation.
[5]Co-treatment for posttransplantation lymphoproliferative disorder.
[6]Includes azathioprine, mycophenolate sodium, and mycophenolate mofetil.
[7]Includes calcineurin inhibitor, antiproliferative agent, and corticosteroid.
[8]Includes cyclosporin A and tacrolimus.
[9]Includes sirolimus and everolimus.

the eligibility criteria, and 509 (kidney, n = 295; liver, n = 214) agreed to participate (see Supplementary Figure S1 online). Main reasons for refusal were prior time commitments, living remotely, or already seeing a private dermatologist. Most (60%) ineligible patients were excluded because of dark skin color (not of European ancestry); the remainder had serious comorbidity. There were no differences by age, sex, and numbers of years of immunosuppression between consenting and nonconsenting patients. The current analysis was based on 495 (97%) participants who had undergone the baseline skin examination. Of these, 42 did not complete the self-administered questionnaire and so were not included in the multivariable analyses. Skin cancer prevalence was no different in those who completed the questionnaire and those who did not.

The average ages of kidney and liver transplant recipients were very similar despite differences in their age distributions (Table 1). More kidney than liver transplant recipients were fair skinned, had skin cancer treated in the past 2 years, underwent full skin checks more than once a year, and received transplants longer than 20 years ago. Most kidney transplant recipients (84%) were receiving triple immunosuppressive therapy, whereas most liver transplant recipients (73%) were receiving a calcineurin inhibitor, with or without corticosteroids.

In total,135 kidney and liver transplant recipients had 168 histopathologically confirmed skin cancers (50 BCCs, 41 SCCs, 77 Bowen's disease) in the baseline 3 months (Table 2), giving a 27% period prevalence. Multivariable analyses conducted separately for BCC and SCC and by organ transplant type showed no statistically significant differences in the magnitude of the effect estimates or the characteristics independently associated with each skin cancer type. Therefore, adjusted prevalence ratios (PRs) are presented for the combined outcomes of BCC or SCC in both kidney and liver transplant patients. Self-reported history of skin cancer in the previous 2 years was the factor most strongly associated with prevalence of BCC or SCC (prevalence ratio = 3.39, 95% confidence interval = [1.93, 5.95]), followed by frequent whole-body skin checks (more than annually), fair complexion, and being born in Australia (Table 3).

Table 2. Prevalence of skin cancers and related tumors in 495 organ transplant recipients with completed baseline clinical skin examination

Lesion Types	Kidney (n = 287), n (%)	Liver (n = 208), n (%)
Basal cell carcinoma		
No	257 (90)	188 (90)
Yes	30 (10)	20 (10)
Single	25 (9)	12 (6)
Multiple	5 (1)	8 (4)
Number of individual tumors	40 (14)	31 (15)
Squamous cell carcinoma		
No	255 (89)	190 (91)
Yes	32 (11)	18 (9)
Single	25 (9)	16 (8)
Multiple	7 (2)	2 (1)
Number of individual tumors	43 (15)	22 (11)
Bowen's Disease (IEC)		
No	236 (82)	182 (87)
Yes	51 (18)	26 (13)
Single	28 (10)	17 (8)
Multiple	23 (8)	9 (5)
Number of individual tumors	107 (37)	51 (25)
Other skin cancers[1]		
No	283 (99)	204 (98)
Yes	4 (1)	4 (2)
Single	4 (1)	4 (2)
Multiple	0 (0)	0 (0)
Number of individual tumors	4 (1)	4 (2)
Any skin cancer[2]		
No	205 (71)	155 (75)
Yes[3]	82 (29)	53 (25)
Actinic keratosis		
No	57 (20)	35 (17)
Yes	230 (80)	173 (83)
1–2	98 (34)	76 (37)
3–4	36 (13)	39 (19)
≥5	96 (33)	58 (28)

Abbreviation: IEC, intraepidermal carcinoma.
[1]Includes melanoma (n = 1), keratoacanthoma, and unspecified rare skin conditions.
[2]Includes any histopathologically confirmed skin cancer.
[3]"Yes" estimates for "Any skin cancer" includes OTRs with several different types of prevalent skin cancer.

Table 3. Multivariate analysis for the prevalence of basal cell carcinoma and squamous cell carcinoma combined in organ transplant patients

Characteristics[1]	Prevalent Skin Cancer: No (n = 405), n (%)	Prevalent Skin Cancer: Yes (n = 90), n (%)	PR [95% CI][2]
Transplant type[3]			
Kidney	232 (57)	55 (61)	1.00 (reference)
Liver	173 (43)	35 (39)	0.82 [0.56, 1.18]
Born in Australia			
No	92 (25)	10 (12)	1.00 (reference)
Yes	278 (75)	73 (88)	2.38 [1.28, 4.42]
Natural complexion			
Olive/medium	165 (42)	25 (28)	1.00 (reference)
Fair	230 (58)	65 (72)	1.61 [1.07, 2.43]
Skin reaction to acute sun			
Only tan	92 (25)	18 (22)	1.00 (reference)
Burn then tan	195 (53)	40 (48)	1.14 [0.70, 1.87]
Always burn	82 (22)	25 (30)	1.62 [0.96, 2.75]
Presence of elastosis of neck			
None/mild	237 (60)	32 (36)	1.00 (reference)
Moderate/ high	159 (40)	58 (64)	1.33 [0.87, 2.05]
Past skin cancers in last 2 years			
No	200 (54)	14 (17)	1.00 (reference)
Yes	170 (46)	69 (83)	3.39 [1.93, 5.95]
Frequency of skin checks			
Less than once a year	201 (54)	29 (35)	1.00 (reference)
Once a year	58 (16)	8 (10)	0.86 [0.42, 1.78]
More than once a year	111 (30)	46 (55)	1.76 [1.15, 2.70]
Number protection measures used for sun exposure			
<2	184 (50)	33 (40)	1.00 (reference)
2+	186 (50)	50 (60)	1.36 [0.92, 1.99]
Time in years since first transplant			
1–10	231 (57)	48 (53)	1.00 (reference)
>10–20	126 (31)	30 (33)	1.23 [0.83, 1.82]
>20	48 (12)	12 (13)	1.34 [0.78, 2.29]

Abbreviations: CI, confidence interval; PR, prevalence ratio.
[1]Percentages do not add to 100% because of missing values.
[2]Adjusted for age, sex, and transplant type.
[3]Adjusted for age and sex.

DISCUSSION

We have estimated that around 25% of high-risk kidney and liver transplant recipients in Queensland have a histopathologically confirmed skin cancer at a given time; this is around 3 times higher than the skin cancer prevalence observed in the general population of Queensland when considering individuals also aged over 40 years and who are white (Green et al., 1988). Skin cancer prevalence was similar in both transplant groups in the current study, despite lower levels of immunosuppression in liver transplant recipients in Queensland and other populations (Hirose and Otley, 2008). Because skin cancer prevalence is the net result of incidence versus treatment rates, this similarity of skin cancer prevalence suggests that liver transplant recipients have substantially lower treatment rates of skin cancer than kidney transplant recipients; this is supported by the significantly lower rates of skin cancer surveillance reported by liver transplant recipients in this study.

As expected, our estimate of AK prevalence is far higher than the 54% reported among kidney transplant patients living in more temperate France (Euvrard et al., 1995). To our knowledge, no other reports of AK prevalence in transplant recipients are available. Early treatment of those most heavily affected by AKs has the potential benefit of reducing the risk of malignant transformation (Wallingford et al., 2015; Werner et al., 2013).

Personal characteristics associated with presence of skin cancer in OTRs were confirmed to be the same as for the general population (Green et al., 1988; Kricker et al., 1991). Frequent skin checks were also associated with skin cancer prevalence, consistent with the assumption that the most

severely affected OTRs will also be those receiving medical attention and skin cancer surveillance most frequently. Current international guidelines (Hofbauer et al., 2009) recommend that all OTRs receive annual skin examinations and more frequently in the presence of known skin cancer risk factors (Green et al., 1988). Currently, there are no official guidelines established for routine skin surveillance of OTRs in the Australian health system. Establishing freely accessible, dedicated skin clinics in the future would not only provide routine and timely skin surveillance but also provide the opportunity to educate OTRs intensively about sun protection measures for primary prevention of skin cancer (Hofbauer et al., 2009) and the value of early detection.

Strengths of this study were its large sample size and skin cancer screening examinations of all OTRs in the study by dermatologically trained physicians, along with histopathological verification of suspicious tumors. Our prevalence figures are underestimates, however, because skin cancers that were treated with destructive measures such as cryotherapy were noted but not included in our reported estimates. Secondly, the slightly longer duration of immunosuppression among nonparticipants meant possible underestimation of the true prevalence in this very—high-risk population.

In summary, we have provided an up-to-date quantification of the high burden of skin cancer among high-risk Australian kidney and liver transplant recipients. To decrease the day-to-day skin cancer burden in this vulnerable patient population, available resources need to be optimized to provide intense surveillance, treatment, and primary prevention programs.

MATERIALS AND METHODS

Study population

Participants in the Skin Tumours in Allograft Recipients (STAR) study were high-risk kidney and liver transplant recipients treated at the Princess Alexandra Hospital in Brisbane, Queensland, Australia from November 2012 to June 2014. *High-risk OTRs* were defined as (i) aged 18 years or older, not innately dark/black skinned, immunosuppressed for at least 1 year, and reporting a history of skin cancer or AKs—or, if no history of skin cancer or AKs, (ii) aged 40 years or older or (iii) at least 10 years' duration of immunosuppression. Patients were excluded if they could not provide consent, were undergoing treatment with systemic retinoid therapy, had field treatments with topical agents in the last 6 months, or had concomitant major illness. Study protocols were approved by institutional and hospital Human Research Ethics Committees (HREC/12/QPAH/409; QIMR P1481) and are in agreement with the guidelines set forth by Declaration of Helsinki. All study participants provided written informed consent.

Data collection

All study participants underwent a whole-body skin examination by a dermatologically-trained physician who mapped the location of any suspected skin cancers—BCCs, SCCs, Bowen's disease (intraepidermal carcinoma), melanoma, and Merkel's cell carcinoma—as well as AKs. OTRs with any suspected malignant lesions were referred for definitive management and then recontacted to ascertain outcome of clinical follow-up. Final diagnosis of skin cancer was based on a histopathological diagnosis confirmed within a 3-month baseline period.

Standard skin cancer risk factors were collected by self-administered questionnaire. Medical charts were reviewed to obtain information on date(s) of transplantation(s) and current immunosuppressive therapy regimens.

Statistical analysis

The period prevalence of BCC, SCC, Bowen's disease (intraepidermal carcinoma), and of all malignant skin tumors combined was estimated as the proportion of patients with at least one histopathological diagnosis of the relevant type of skin cancer at baseline skin examination or in the next 3 months, to allow for histopathological confirmation of clinical diagnoses made at the baseline examination and in the immediate aftermath. Period prevalence estimates were calculated separately for kidney and liver transplant patients.

Log binomial regression models for binary outcomes were used to identify characteristics associated with skin cancer prevalence. The prevalence ratio is the ratio of the probability of an event at various levels of the exposure of interest and provides a better estimate of the risk ratio in cross-sectional analyses (Thompson et al., 1998). All factors significant at the 5% level were considered statistically significant. Analyses were performed using SAS (version 9.2, SAS Institute, Cary, NC, USA).

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary Material is linked to the online version of the paper at www.jidonline.org, and at http://dx.doi.org/10.1016/j.jid.2016.02.804.

REFERENCES

Berg D, Otley CC. Skin cancer in organ transplant recipients: Epidemiology, pathogenesis, and management. J Am Acad Dermatol 2002;47:1–20.

Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. New Engl J Med 2003;348:1681–91.

Euvrard S, Kanitakis J, Pouteil-Noble C, Dureau G, Touraine JL, Faure M, et al. Comparative epidemiologic study of premalignant and malignant epithelial cutaneous lesions developing after kidney and heart transplantation. J Am Acad Dermatol 1995;33:222–9.

Fortina AB, Caforio AL, Piaserico S, Alaibac M, Tona F, Feltrin G, et al. Skin cancer in heart transplant recipients: frequency and risk factor analysis. J Heart Lung Transplant 2000;19:249–55.

Fransen M, Karahalios A, Sharma N, English DR, Giles GG, Sinclair RD. Non-melanoma skin cancer in Australia. Med J Aust 2012;197:565–8.

Green A, Beardmore G, Hart V, Leslie D, Marks R, Staines D. Skin cancer in a Queensland population. J Am Acad Dermatol 1988;19:1045–52.

Haagsma EB, Hagens VE, Schaapveld M, van den Berg AP, de Vries EG, Klompmaker IJ, et al. Increased cancer risk after liver transplantation: a population-based study. J Hepatol 2001;34:84–91.

Hirose R, Otley C. Allograft-specific considerations in transplant dermatology. In: Otley CC, Stasko T, editors. Skin disease in organ transplantation. Cambridge: Cambridge Press; 2008, p. 39–45.

Hofbauer GF, Anliker M, Arnold A, Binet I, Hunger R, Kempf W, et al. Swiss clinical practice guidelines for skin cancer in organ transplant recipients. Swiss Med Wkly 2009;139:407–15.

Kricker A, Armstrong BK, English DR, Heenan PJ. Pigmentary and cutaneous risk factors for non-melanocytic skin cancer—a case-control study. Int J Cancer 1991;48:650–62.

Mackenzie KA, Wells JE, Lynn KL, Simcock JW, Robinson BA, Roake JA, et al. First and subsequent nonmelanoma skin cancers: incidence and predictors in a population of New Zealand renal transplant recipients. Nephrol Dial Transplant 2010;25:300–6.

Martin HL, Chen JW, Koczwara B. Cancer in liver transplant recipients: management and outcomes. Asia Pac J Clin Oncol 2013;9:257–64.

Ramsay HM, Fryer AA, Hawley CM, Smith AG, Harden PN. Non-melanoma skin cancer risk in the Queensland renal transplant population. Br J Dermatol 2002;147:950–6.

Ruegg CP, Graf N, Muhleisen B, Szucs TD, French LE, Surber C, et al. Squamous cell carcinoma of the skin induces considerable sustained cost of care in organ transplant recipients. J Am Acad Dermatol 2012;67:1242–9.

Thompson ML, Myers JE, Kriebel D. Prevalence odds ratio or prevalence ratio in the analysis of cross sectional data: what is to be done? Occup Environ Med 1998;55:272–7.

Wallingford SC, Russell SA, Vail A, Proby CM, Lear JT, Green AC. Actinic keratoses, actinic field change and associations with squamous cell carcinoma in renal transplant recipients in Manchester, UK. Acta Derm Venereol 2015;95:830–4.

Werner RN, Sammain A, Erdmann R, Hartmann V, Stockfleth E, Nast A. The natural history of actinic keratosis: a systematic review. Br J Dermatol 2013;169:502–18.

Zavos G, Karidis NP, Tsourouflis G, Bokos J, Diles K, Sotirchos G, et al. Nonmelanoma skin cancer after renal transplantation: a single-center experience in 1736 transplantations. Int J Dermatol 2011;50:1496–500.