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Prevalence of skin cancer and related skin tumors in high-risk kidney and liver transplant recipients in Queensland, Australia

Iannacone MR[1*], Sinnya S[2*], Pandeya N[3], Isbel N[4], Campbell S[4], Fawcett J[5], Soyer HP[2], Ferguson L[1], Davis M[1], Whiteman DC[1], STAR Study†, Green AC[1,6]

[1] QIMR Berghofer Medical Research Institute, Population Health, Queensland, Australia

[2]Dermatology Research Centre, University of Queensland, School of Medicine, Translational Research Institute, Queensland, Australia

[3]School of Public Health, University of Queensland, Queensland, Australia

[4]Department of Nephrology, University of Queensland, Princess Alexandra Hospital, Queensland, Australia

[5]Queensland Liver Transplant Service, University of Queensland, Princess Alexandra Hospital, Queensland, Australia

[6]Cancer Research UK Manchester Institute and Institute of Inflammation and Repair, University of Manchester, Manchester, United Kingdom

*Co-first authors

† See Appendix

Author correspondence to:

Professor Adèle C. Green, QIMR Berghofer Medical Research Institute

Locked Bag 2000 Royal Brisbane Hospital, QLD 4029, Australia

Email: Adele.Green@qimrberghofer.edu.au

Running Title: Skin cancer prevalence in OTRs

Abbreviations: actinic keratosis (AK); basal cell carcinoma (BCC); Bowen Disease (BD); confidence interval (CI); intra-epidermal carcinoma (IEC); keratinocyte cancer (KC); merkel cell carcinoma (MCC); organ transplant recipient (OTR); Skin Tumours in Allograft Recipients (STAR); standard deviation (SD); squamous cell carcinoma (SCC)

ABSTRACT

The increased skin cancer incidence in organ transplant recipients (OTRs) 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 (AKs) in high-risk kidney and liver transplant recipients and assess associated factors. OTRs underwent full skin examinations by dermatologically-trained physicians. The proportion of examined OTRs with histopathologically-confirmed skin cancer in the 3-month baseline period was estimated. Prevalence ratios (PR) with 95% confidence intervals (CIs) indicated significant associations. Of 495 high-risk OTRs (average age 54, immunosuppressed 8.9 years), 135 (27%) had basal cell carcinoma, squamous cell carcinoma or Bowen Disease (intra-epidermal carcinoma) present and confirmed in the baseline period with respective prevalence proportions of 10%, 11%, and 18% in kidney recipients and 10%, 9% and 13% in liver transplant recipients. Over 80% had AKs present with approximately 30% having $\geq$5AKs. OTRs with the highest skin cancer burden were Australian-born; fair-skinned (PR=1.61, 1.07-2.43); reported past skin cancer (PR=3.39, 95% CI=1.93-5.95); and were receiving the most frequent skin checks (PR=1.76, 95% CI=1.15-2.70). In conclusion, high-risk OTRs carry a substantial measurable skin cancer burden at any given time and require frequent review through easily accessible, specialized services.

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 rises with advances in surgery and improved immunosuppressive drug regimens, so too does the burden of these keratinocyte cancers (KC) (Berg and Otley, 2002; Euvrard *et al.*, 2003) and the associated health-care costs (Fransen *et al.*, 2012; Ruegg *et al.*, 2012).

To date cumulative incidence rates of skin cancer following 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 disease present in a given time window, provides a measure of the net effects of incidence and treatment. 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 AK baseline prevalence, in kidney and liver transplant recipients in Queensland. We assessed those at 'high-risk' of KC since these are the OTRs who carry most of the skin cancer burden in a community. We also assessed risk factors associated with having KC present on the skin in this period.

Results

Of 735 kidney and 394 liver transplant patients attending Princess Alexandra Hospital, 749 (kidney: 464; liver: 285) met the eligibility criteria and 509 (kidney: 295; liver: 214) agreed to participate (Figure S1). 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 non-consenting 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 >20 years ago. The majority of kidney (84%) transplant recipients were receiving triple immunosuppressive therapy, while 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 BD) 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 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 (PR=3.39; 95% CI=1.93-5.95), followed by frequent whole-body skin checks (more than annually), fair complexion and being born in Australia (Table 3).

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 White (i.e. of Caucasian descent) (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). Since skin cancer prevalence is the net result of incidence vs 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). 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 above 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 non-participants meant possible underestimation of the true prevalence in this ultra-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, from November, 2012 to June, 2014. 'High-risk' OTRs were defined as 1) aged ≥18 years, not innately dark/black-skinned, immunosuppressed for ≥1 year and reporting a history of skin cancer or AKs; or, if no history of skin cancer or AKs, 2) aged ≥40 years or 3) ≥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 Disease (BD) (intra-epidermal carcinoma (IEC)), melanoma, Merkel cell carcinoma (MCC), as well as AKs. OTRs with any suspected malignant lesions were referred for definitive management and then re-contacted to ascertain outcome of clinical follow-up. Final diagnosis of skin cancer was based on a histopathologic 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, BD (IEC), 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 (PR) 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).

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *Journal of Investigative Dermatology*.

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STAR Study team

Scott Campbell, Daniel Chambers, Marcia Davis, Jonathan Fawcett, Lisa Ferguson, Michelle Grant, Adele Green, Carmel Hawley, Peter Hopkins, Nicole Isbel, Michelle Iannacone, Therese Lawton, Diana Leary, Kyoko Miura, Tom Olsen, Nirmala Pandeya, Natalie Ong, Azadeh Sahebian, Sudipta Sinnya, H. Peter Soyer, Jean M. Tan, Mandy Way, David Whiteman

References

Berg D, Otley CC (2002) Skin cancer in organ transplant recipients: Epidemiology, pathogenesis, and management. *Journal of the American Academy of Dermatology* 47:1-17; quiz 8-20.

Euvrard S, Kanitakis J, Claudy A (2003) Skin cancers after organ transplantation. *The New England journal of medicine* 348:1681-91.

Euvrard S, Kanitakis J, Pouteil-Noble C, Dureau G, Touraine JL, Faure M, *et al.* (1995) Comparative epidemiologic study of premalignant and malignant epithelial cutaneous lesions developing after kidney and heart transplantation. *Journal of the American Academy of Dermatology* 33:222-9.

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

Fransen M, Karahalios A, Sharma N, English DR, Giles GG, Sinclair RD (2012) Non-melanoma skin cancer in Australia. *The Medical journal of Australia* 197:565-8.

Green A, Beardmore G, Hart V, Leslie D, Marks R, Staines D (1988) Skin cancer in a Queensland population. *Journal of the American Academy of Dermatology* 19:1045-52.

Haagsma EB, Hagens VE, Schaapveld M, van den Berg AP, de Vries EG, Klompmaker IJ, *et al.* (2001) Increased cancer risk after liver transplantation: a population-based study. *Journal of hepatology* 34:84-91.

Hirose R, Otley C (2008) Allograft-Specific Considerations in Transplant Dermatology In: Otley CC ST (ed) Skin Disease in Organ Transplantation. Cambridge Press, Cambridge.

Hofbauer GF, Anliker M, Arnold A, Binet I, Hunger R, Kempf W, *et al.* (2009) Swiss clinical practice guidelines for skin cancer in organ transplant recipients. *Swiss medical weekly* 139:407-15.

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

Mackenzie KA, Wells JE, Lynn KL, Simcock JW, Robinson BA, Roake JA, *et al.* (2010) First and subsequent nonmelanoma skin cancers: incidence and predictors in a population of New Zealand renal transplant recipients. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 25:300-6.

Martin HL, Chen JW, Koczwara B (2013) Cancer in liver transplant recipients: management and outcomes. *Asia-Pacific journal of clinical oncology* 9:257-64.

Ramsay HM, Fryer AA, Hawley CM, Smith AG, Harden PN (2002) Non-melanoma skin cancer risk in the Queensland renal transplant population. *The British journal of dermatology* 147:950-6.

Ruegg CP, Graf N, Muhleisen B, Szucs TD, French LE, Surber C, *et al.* (2012) Squamous cell carcinoma of the skin induces considerable sustained cost of care in organ transplant recipients. *Journal of the American Academy of Dermatology* 67:1242-9.

Thompson ML, Myers JE, Kriebel D (1998) Prevalence odds ratio or prevalence ratio in the analysis of cross sectional data: what is to be done? *Occupational and environmental medicine* 55:272-7.

Wallingford SC, Russell SA, Vail A, Proby CM, Lear JT, Green AC (2015) Actinic Keratoses, Actinic Field Change and Associations with Squamous Cell Carcinoma in Renal Transplant Recipients in Manchester, UK. *Acta dermato-venereologica*.

Werner RN, Sammain A, Erdmann R, Hartmann V, Stockfleth E, Nast A (2013) The natural history of actinic keratosis: a systematic review. *The British journal of dermatology* 169:502-18.

Zavos G, Karidis NP, Tsourouflis G, Bokos J, Diles K, Sotirchos G, *et al.* (2011) Nonmelanoma skin cancer after renal transplantation: a single-center experience in 1736 transplantations. *International journal of dermatology* 50:1496-500.

Table 1. Personal characteristics of 495 organ transplant recipients

Characteristics[1]	Kidney (n=287) n (%)	Liver (n=208) n (%)	p[2]
Age (in years)			
Mean (S.D)	54 (11)	55 (13)	
<40	30 (10)	27 (13)	
40 – 49	66 (23)	21 (10)	
50 – 59	79 (28)	74 (36)	
60 – 69	95 (33)	71 (34)	
70 +	17 (6)	15 (7)	0.001
Sex			
Female	105 (37)	75 (36)	
Male	182 (63)	133 (64)	0.90
Born in Australia			
No	55 (21)	47 (25)	
Yes	208 (79)	143 (75)	0.34
Natural complexion			
Olive / medium	102 (36)	88 (44)	
Fair	182 (64)	113 (56)	0.08
Skin reaction to acute sun			
Only tan	59 (23)	51 (27)	
Burn then tan	132 (50)	103 (54)	
Always burn	72 (27)	35 (19)	0.08
Presence of elastosis of neck			
None	28 (10)	22 (11)	
Little	134 (47)	85 (43)	
Moderate	112 (39)	81 (40)	
High	11 (4)	13 (6)	0.50
Past skin cancers (last 2 yrs)[3]			
No	111 (42)	103 (54)	
Yes	152 (58)	87 (46)	0.01
Frequency of skin checks (last 5 yrs)			
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 protection measures used for sun exposure			
<2	120 (46)	97 (51)	
2+	143 (54)	93 (49)	0.25
Time (yrs) since first transplant[4]			
Mean (S.D.)	11 (9)	9 (7)	
1-5	90 (31)	71 (34)	
>5-10	65 (23)	53 (25)	
>10-20	88 (31)	68 (33)	
>20	44 (15)	16 (8)	0.08
Immunosupressive therapy regimens			
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)

[1]Columns do not add to 100% due to 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 post transplantation lymphoproliferative disorder

[6]Includes azathioprine, mycophenolate sodium and mycophenolate mofetil

[7]Includes calcineurin inhibitor, antiproliferative agent and corticosteroid

[8]Includes cyclosporin A and tacromilus

[9]Includes sirolimus and everolimus

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)
# 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)
# of individual tumors	43 (15)	22 (11)
Bowen Disease (IEC)		
No	236 (82)	182 (87)
Yes	51 (18)	26 (13)
Single	28 (10)	17 (8)
Multiple	23 (8)	9 (5)
# 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)
# 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)

[1]Includes melanoma (n=1), keratoacanthoma, 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 prevlanet skin cancer

Table 3. Multivariate analysis for the prevalence of BCC and SCC combined in organ transplant patients

	Prevalent Skin Cancer		
	No (n=405)	Yes (n=90)	
Characteristics[1]	**n (%)**	**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 (last 2 yrs)			
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 (yrs) 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)

[1]Columns do not add to 100% due to missing values

[2]Adjusted for age, sex and transplant type

[3]Adjusted for age and sex