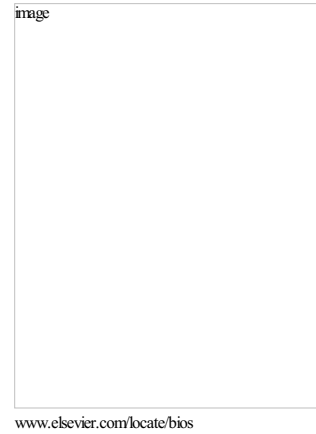


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HIGH PREVALENCE OF SKIN CANCERS AND ACTINIC KERATOSES IN LUNG TRANSPLANT RECIPIENTS

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Increased risk of malignancy is a major complication of lung transplantation. Keratinocyte cancers (KC), namely cutaneous squamous cell cancers (SCCs) and basal cell cancers (BCCs), are a particular risk, and cause high morbidity and some mortality among lung transplant recipients (LTRs) (1). Actinic keratoses (AKs) are potentially premalignant skin lesions strongly associated with SCC although the AK burden in LTR has not been specifically measured. The heightened risks of skin cancer and AKs are due to two main factors, high-dose immunosuppression and sun exposure, but their relative contributions are unknown. To assess the burden of skin cancer and AKs in LTRs at a point in time in a high sun exposure region, we therefore conducted a cross-sectional study and estimated the prevalence of skin cancer and AKs in LTRs in the state of Queensland, Australia.

The study was approved by Institutional Ethics Committees. We invited LTRs aged over 17 to participate during routine clinics (July 2012-July 2013) at The Prince Charles Hospital, the only treatment centre for LTR in the state. Participants provided information via a self-completed questionnaire (2) about standard risk factors for skin cancer (age, sex, skin phototype, past sun exposure, smoking, history of previous skin cancer). They underwent a full skin examination by a dermatology-trained physician who mapped the location of all lesions clinically suspicious for malignancy and of AKs, and visually graded the severity of neck solar elastosis. LTRs were referred to their doctor for histopathologic diagnosis of suspicious lesions (usually available within 3 months). Information on date of transplant, current immunosuppressive therapy and use of voriconazole (risk factor for SCC (3)) were obtained by medical chart review. We calculated period prevalences of skin cancers based on malignant lesions histopathologically-confirmed within 3 months of examination. Site-specific AK counts were summed to give total AK prevalence at baseline. Logistic regression was used to assess associations with the composite outcome of having either skin cancer or >5AKs present on the skin in a multivariable model adjusting for all potential confounding factors.

Of 191 LTRs aged over 17 in Queensland, 159 were approached and 122 (77%) participated with informed, written consent (Supp Figure). Non-participants were similar to participants in age and sex but had longer mean time from transplantation (6.8 years vs 4.7 years). Average age of LTRs

studied was 50 years and 93% used triple therapy immunosuppression (calcineurin inhibitor, antimetabolite, corticosteroid). Half the participants had fair skin, 22% had moderate or severe solar elastosis and 44% reported past skin cancer (15% pre-transplant).

There were 44 confirmed skin cancers (7 BCCs, 20 SCCs, 16 intraepithelial carcinomas (IECs), 1 melanoma) in the 3-month baseline period and 9 LTRs (7%) had multiple (33) BCCs, SCCs or IECs present on the skin (Table 1). Corresponding prevalences of BCC, SCC and total skin cancer were 5%, 8% and 13% respectively. Of the 122 LTRs examined, 74 (61%) had one or more AKs present, and a third had >5 AKs. In a multivariable model adjusted for all potential confounding factors, we found that categories of increasing severity of solar elastosis of the neck and a history of previous KC were associated with having either skin cancer or >5AKs present on the skin at examination (Table 2). While odds of KC or >5AK almost doubled with voriconazole treatment (adjusted OR 1.8) this was not statistically significant. Odds of KC or >5AK increased with increasing transplant duration (Table 2) (and this was true for AK and KC separately, though sparse numbers limited the precision of estimated ORs).

One previous study of KC in LTRs showed similar transplant-related risk factors but it assessed incidence over time (rather than prevalence that indicates necessary outlay of treatment services) and did not assess sun exposure (1). No other generalizable, population-based data on skin cancer and AK prevalence and role of sun exposure are available for LTRs, though small numbers of prevalent KC limited our statistical power. The composite endpoint may have diluted KC associations. Skin cancer prevalence of 13% in Queensland LTRs is far more than the 5% in the general population aged 20-69 (4). The 61% AK prevalence alone is notably higher than 42% with AK or skin cancer in referred French organ transplant recipients (5). Still our figures may substantially underestimate the burden in Queensland LTRs because of longer transplant duration in non-participants, and because the study did not count as outcome events the non-histologically confirmed skin tumors that were destructively treated (eg cryotherapy and 5-fluorouracil).

Our results provide further evidence of the association between sun exposure and skin carcinogenesis in LTRs and we therefore vigorously encourage LTRs' use of sun protection. We also support the establishment of dedicated, specialist skin cancer surveillance clinics and curative treatment of AKs.

Financial conflict of interest disclosure

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References:

1. Rashtak S, Dierkhising RA, Kremers WK, Peters SG, Cassivi SD, Otley CC: Incidence and risk factors for skin cancer following lung transplantation. *J Am Acad Dermatol* 2015;72:92-8.
2. Morze CJ, Olsen CM, Perry SL, et al.: Good test-retest reproducibility for an instrument to capture self-reported melanoma risk factors. *Journal of clinical epidemiology* 2012;65:1329-36.
3. Mansh M, Binstock M, Williams K, et al.: Voriconazole Exposure and Risk of Cutaneous Squamous Cell Carcinoma, Aspergillus Colonization, Invasive Aspergillosis and Death in Lung Transplant Recipients. *American Journal of Transplantation* 2016;16:262-70.
4. 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.
5. Euvrard S, Kanitakis J, Pouteil-Noble C, 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.

Table 1. Prevalence of skin cancer and AKs in 122 lung transplant recipients

	N (%)
Basal Cell Carcinoma	
No	116
Yes	6 (5)
Single BCC	5 (4)
Multiple BCC	1 (0.8)
Number of individual tumors	7
Squamous Cell Carcinoma	
No	112
Yes	10 (8)
Single	6 (5)
Multiple	4 (3)
Number of individual tumors	20
Intra-epidermal carcinoma (IEC)	
No	117
Yes	5 (4)
Single	1 (0.8)
Multiple	4 (3)
Number of individual tumors	16
Melanoma	
No	121 (99)
Yes	1 (0.8)
Any skin cancer (BCC,SCC, IEC or Melanoma)	
No	107 (88)
Yes	15 (13)
Number of individual tumors	44

Total number of AKs†

None	47 (39)
1-5	34 (28)
>5	40 (33)

†121 lung transplant recipients (one excluded due to missing AK data)

Table 2. Joint prevalence of skin cancer and AKs and associated factors in 121‡ lung transplant recipients

	Joint skin cancer and AK status		Multivariable adjusted odds ratio§
	No skin cancer ≤5 AKs	Skin cancer or >5 AKs	
Age group	N (%)	N (%)	
<50	42 (54)	10 (23)	Reference
50-59	20 (26)	14 (33)	1.2 (0.2 – 6.5)
60 or more	16 (21)	19 (44)	1.2 (0.2 – 7.4)
Sex			
Female	38 (49)	13 (30)	Reference
Male	40 (51)	30 (70)	1.6 (0.5 – 4.7)
Duration of transplant			
0-2 years	37 (47)	14 (33)	Reference
>2-5 years	14 (18)	8 (19)	2.0 (0.4 – 10.8)
>5 years	27 (35)	21 (49)	2.8 (0.6 – 12.6)
Voriconazole			
Never	33 (42)	17 (40)	Reference
Ever	45 (58)	26 (60)	1.8 (0.6 – 5.0)
Skin color			
Dark	11 (14)	4 (9)	Reference
Medium	29 (38)	16 (36)	1.4 (0.2 – 9.5)
Fair	37 (48)	23 (53)	2.6 (0.3– 20.8)

Solar elastosis of neck			
None	30 (39)	1 (2)	Reference
Mild	34 (45)	28 (65)	24.8 (1.9 – 321.7)
Moderate or severe	12 (16)	14 (33)	35.5 (2.0 – 628.7)
Sunburn history			
Never	5 (6)	6 (15)	Reference
1-10	55 (71)	23 (56)	0.3 (0.04 – 2.4)
>10	17 (22)	12 (29)	0.5 (0.06 – 4.8)
Frequency of skin checks			
No routine	34 (44)	17 (40)	Reference
Annually or less	24 (31)	7 (16)	0.2 (0.03 – 0.9)
More than annually	19 (25)	19 (44)	0.3 (0.05 – 1.7)
Sunscreen use (past year)			
None/<50% of the time outdoors	39 (51)	27 (63)	Reference
>50% of the time outdoors	38 (49)	16 (37)	0.9 (0.3 – 3.4)
Hat use (past year)			
None or <50% of the time outdoors	28 (37)	12 (28)	Reference
>50% of the time outdoors	48 (63)	31 (72)	1.6 (0.5 – 5.5)
Previous history of skin cancer			
No	55 (71)	10 (23)	Reference
Yes	23 (29)	33 (77)	5.6 (1.6 – 19.3)

‡121 lung transplant recipients (one excluded due to extensive missing data)

§ Adjusted for all variables in table