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Skin cancer multiplicity in lung transplant recipients: a prospective population-based study

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Summary

Background Lung transplant recipients are at high risk of skin cancer, but precise annual incidence rates of treated skin cancers per patient are unknown.
Objectives To perform a prospective assessment of the total burden of histologically confirmed squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) and associated factors in lung transplant recipients.
Methods A population-based cohort of 125 Queensland lung transplant recipients aged 18 years and over, recruited between 2013 and 2015, were followed to the end of 2016. All underwent dermatological skin examinations at baseline and annually thereafter and patients self-reported all interim treated skin cancers, which were verified against pathology databases. Standard skin cancer risk factors were obtained via questionnaire, and details of medications were acquired from hospital records.
Results During a median follow-up time of 1·7 years, 29 (23%) and 30 (24%) lung transplant recipients with a median duration of immunosuppression of 3·3 years developed SCC and BCC, respectively. The general population age-standardized incidence rates of SCC and BCC were 201 and 171 per 1000 person-years, respectively (based on first primary SCC or BCC during follow-up); however, on accounting for multiple primary tumours, corresponding incidence rates were 447 and 281 per 1000 person-years. Risk of multiple SCCs increased around sixfold in those aged ≥ 60 years and in those with previous skin cancer, and increased around threefold in those treated with the antifungal medication voriconazole. Multiple BCC risk rose threefold from age 60 years and tenfold for patients with previous skin cancer.
Conclusions Lung transplant recipients have very high incidence of multiple primary skin cancers. Close surveillance and assiduous prevention measures are essential.

What is already known about this topic?

- Lung transplant recipients are known to be especially prone to squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) owing to high-dose immunosuppressants, but precise annual incidence rates and skin cancer multiplicity in this high-risk group are unknown.

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Conflicts of interest
None to declare.

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What does this study add?

- We have quantified the burden of new skin cancers developed annually by lung transplant recipients in Queensland, Australia.
- We found an extremely high histologically confirmed SCC tumour burden of 447 per 1000 person-years, and a high BCC tumour burden of 281 per 1000 person-years.
- Multiplicity of SCCs and BCCs increased with age > 60 years and previous skin cancer.
- Multiple SCCs also increased after treatment with the antifungal medication voriconazole.

Keratinocyte skin cancers, namely squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), are known to be relatively common malignancies in organ transplant recipients,[1] but lung transplant recipients are at particularly high risk. Previous studies in Denmark[2] and the U.K.[3] showed that lung transplant recipients developed a new SCC or BCC at more than 10 times the rate seen in the general population. In a series of 166 lung transplant recipients in the Mayo Clinic, 28% developed SCC and 12% developed BCC within 5 years of transplantation,[4] while in a hospital clinic in Sydney, Australia, the corresponding figures were 34% and 17%, respectively.[5] To date, all available estimates have been based either on the first occurrence of SCC or BCC[2,3,5] or on the cumulative incidence of a second skin cancer of the same type as the first,[4] but annual incidence rates are not available. Moreover, like other organ transplant recipients, lung transplant recipients are prone to multiple primary skin cancers,[6–8] but incidence rates of multiple SCCs and BCCs in these high-risk patients have not been studied. While the risk factors for developing a skin cancer in organ transplant recipients include male sex, history of skin cancer, sun-sensitive phenotype and high levels of sun exposure and immunosuppressive drugs[4–6,9,10] and treatment with voriconazole (a fungicidal medication associated with photosensitivity),[11] the risk factors for multiple incident skin cancers in lung transplant recipients have likewise never been investigated.

Besides signifying the sheer tumour burden in affected lung transplant recipients, multiple skin cancers have prognostic significance, as immunosuppressed patients with multiple SCCs appear to have poorer outcomes than those with single tumours.[12] It is therefore clinically important to address these gaps in knowledge about multiple skin cancers in transplant recipients. In a population-based cohort of lung transplant recipients, we estimated the age-standardized incidence rates of SCC and BCC in terms of persons affected and multiplicity of tumours, and we examined the associations between potential risk factors and multiple SCCs and BCCs.

Patients and methods

We prospectively ascertained all lung transplant recipients in Queensland through the only thoracic transplant treatment centre, namely the Prince Charles Hospital, Brisbane. Lung transplant recipients were enrolled in the Skin Tumours in Allograft Recipients study from October 2013 to June 2015 and were followed to June 2016. Eligible lung transplant recipients (age 18 years or older; ≥ 1 year post-transplant; no recent major changes in immunosuppressive therapy) were recruited during their first routine clinic visit in the study period. Patients were excluded if they had commenced systemic retinoid therapy or topical treatments in the previous 6 months. Study procedures were approved by ethics committees of Queensland Health Metro North and Queensland Institute of Medical Research Berghofer Medical Research Institute and all participants provided written informed consent.

Baseline data collection

At recruitment, lung transplant recipients completed a self-administered questionnaire providing general information including: age, sex, education, skin reaction to acute sun exposure, lifetime number of painful sunburns, whether their occupation was mainly indoors or outdoors or mixed, number of usual sun-protection measures used when outdoors, past skin cancer history and frequency of whole-body skin checks by a physician. We obtained clinical information about duration of immunosuppression, immunosuppressive medication and dates of any voriconazole treatment from medical records. All participants underwent a whole-body skin examination by a physician trained in dermatology who documented all clinically diagnosed skin cancers and actinic keratoses on a body map, in addition to natural skin colour and degree of neck elastosis. All patients with suspected skin cancers were referred to their own physicians for management.

Follow-up

Lung transplant recipients received follow-up whole-body dermatological examinations annually during routine clinic visits, using the same protocol as at baseline, until the end of the study period, withdrawal or death. To ensure that all skin cancers treated between skin exams were captured, research staff made telephone calls quarterly to all

participants to ask about skin cancers treated in the previous 3 months, and treating doctors completed treatment cards with details of newly diagnosed lesions. Histopathology reports were obtained for self-reported skin cancers and we routinely checked state and private pathology databases for skin cancers among participants that had not otherwise been reported.

Statistical analysis

Counts of histologically confirmed SCCs (or BCCs) were used to estimate incidence rates of SCCs (or BCCs), age-standardized to the 2001 Australian population. Incidence rates in terms of people affected were estimated by time to first SCC (or BCC) during follow-up divided by person-years (PYs) at risk [defined as years from baseline skin examination to first SCC (or BCC), or for those without a cancer, years from baseline skin examination to end of study, withdrawal or death, whichever came first]. For incidence of new primary SCC (or BCC) tumours, rates were calculated as total number of SCC (or BCC) tumours/PYs at risk.

We investigated associations between baseline characteristics and development of multiple primary skin cancers only, as risk factors for occurrence of first SCC (or BCC) are well established.[4,13] We modelled the number of primary skin cancers using negative binomial regression with offset (total PYs at risk = years from baseline skin examination to end of study, withdrawal or death) to calculate age- and sex-adjusted incidence rate ratios (IRRs) and 95% confidence intervals (CIs). Variables with P-values < 0·2 in the univariate analysis were examined using backward stepwise regression until all variables were significant (at 5% level). All analyses were performed in Stata version 15 (StataCorp, College Station, TX, U.S.A.).

Results

Of 192 eligible lung transplant recipients, 129 agreed to participate (67% response) and four subsequently discontinued, resulting in a cohort of 125. Their average age at recruitment was 50 years, 72 (58%) were male and 28 (24%) had tertiary education (Table 1). Around two-thirds had fair skin (63%), half had mainly outdoor occupations and a further half had experienced multiple sunburns. Median time since transplantation was 3·3 years [interquartile range (IQR) 1·6–7·6]. A majority of patients (n = 94) were receiving mycophenolate mofetil [of whom 24 (26%) developed SCC during the study period] in preference to azathioprine [current treatment for 21 patients, three of whom (14%) developed SCC in the study period], and overall 66% had been treated with voriconazole since transplantation (Table 1) with median exposure of 3·7 months (IQR 2·5–5·5). Most lung transplant recipients (84%) reported no skin cancer prior to their lung transplant, but by the time of enrolment in the present study, 70 recipients (56%) reported a skin cancer history and these patients tended to be older and more likely to have moderate-to-high levels of solar elastosis of the neck on dermatological examination (Table 1).

Incidence of squamous cell carcinoma and basal cell carcinoma

Over a median follow-up time of 1·7 years (IQR 1·4–2·2), 29 lung transplant recipients developed at least one SCC and 30

Table 1 Baseline characteristics of all lung transplant recipients (n = 125) and those with skin cancer history present at study baseline (n = 70)

Characteristic	Total (N = 125) n (%)	Past skin cancer at baseline (n = 70) n (%)
Age group, years		
< 60	90(72)	41(59)
≥ 60	35(28)	29(41)
Sex		
Female	53(42)	24(34)
Male	72(58)	46(66)
Completed education[a]		
Grade 12 or less	57(49)	35(50)
Trade/diploma	32(27)	19(27)
University/college	28(24)	16(23)
Natural skin colour		
Olive/medium	46(37)	27(39)
Fair	79(63)	43(61)
Lifetime painful sunburns[a]		
Up to five times	57(49)	29(41)
More than five times	60(51)	41(59)
Occupational sun exposure[a]		
Mainly indoors	60(51)	31(44)
Both indoors and outdoors/mainly outdoors	57(49)	39(56)
Solar elastosis of neck		
None/little	72(58)	27(39)
Moderate/high	53(42)	43(61)
Skin cancers prior to transplant[a]		
No	87(84)	42(74)
Yes	17(16)	15(26)
Frequency of skin checks[a]		
≤ Once a year	70(60)	33(47)
> Once a year	47(40)	37(53)
Number of sun protection measures usually used[a]		
< 2	48(41)	33(47)
≥ 2	69(59)	37(53)
Number of years immunosuppressed		
1–5	73(58)	36(51)
> 5	52(42)	34(49)
Voriconazole use[b]		
No	43(34)	29(41)
Voriconazole < 4 months	44(38)	19(27)
Voriconazole ≥ 4 months	38(30)	22(31)

[a]Some participants did not provide this information. [b]Total voriconazole exposure since transplant.

developed at least one BCC, giving person-based incidence rates of 201 per 1000 PYs for SCC and 171 per 1000 PYs for BCC (Table 2). In total, 46 lung transplant recipients developed 93 histologically confirmed SCC tumours and 74 histologically confirmed BCCs. Of these 46 lung transplant recipients, 16 developed SCCs only, 17 developed BCCs only and 13 patients developed both. One patient had 11 SCCs, and another patient who developed 25 BCCs also developed eight new SCCs, resulting in a total of 33 keratinocyte cancers, the maximum seen in one lung transplant recipient during the study period. Regarding the frequency of high-risk histological features among the 93 SCCs diagnosed in these patients, 17 (18%) were poorly differentiated, perineural invasion was present in three, and of 79 SCCs with information available on depth of invasion, 36 (46%) had invaded to the level of the reticular dermis and a further 12 (15%) to the subcutaneous fat or beyond. During a median follow-up of 1·4 years (IQR 0·9–1·7), eight participants in the cohort died, but none from keratinocyte cancer, and there were no cases of metastatic SCC in the follow-up period.

Risk factors

After all potential risk factors were examined for associations with multiple incident SCC (or BCC) tumours, the final factors remaining in the multivariable models were age, sex and skin cancer history at study baseline. The strongest predictors of multiple SCCs were skin cancer history at baseline (IRR 6·9, 95% CI 2·0–23·9), age ≥ 60 years (IRR 6·6, 95% CI 2·9–15·2) (Table 3) and ever having received treatment with voriconazole (IRR 2·7, 95% CI 1·1–7·1). Duration of voriconazole treatment was also associated with multiple SCCs; compared with never use, IRR after < 4 months of treatment was 1·9 (95% CI 0·6–5·4) and for voriconazole treatment ≥ 4 months IRR for multiple SCCs was 4·5 (95% CI 1·3–15·3) (Table 3). Male sex (IRR 2·4, 95% CI 0·9–6·1) and moderate-to-high neck elastosis (IRR 2·2, 95% CI 0·8–5·9) were also positively associated (Table 3). For multiple BCCs, skin cancer history at baseline (IRR 10·5, 95% CI 2·2–51·7) and age ≥ 60 years (IRR 3·1, 95% CI 1·3–7·7) were the strongest risk factors, with male sex (IRR 2·2, 95% CI 0·8–6·2) and frequency of skin checks more than once a year (IRR 2·1, 95% CI 0·8–5·3) also showing positive associations (Table 3). Treatment with voriconazole was not associated with multiple BCCs. Duration of immunosuppression (i.e. time since transplantation) was not associated with either BCC or SCC multiplicity.

Table 2 Incidence of skin cancers in terms of people and tumours

Skin cancer	Persons	Tumours
Squamous cell carcinoma		
Number	29	93
Incidence per 1000 PYs (95% CI)	201 (73–329)	447 (311–521)
Basal cell carcinoma		
Number	30	74
Incidence per 1000 PYs (95% CI)	171 (70–272)	281 (183–379)

PYs, person-years; CI, confidence interval.

Discussion

This is the first quantification of the skin cancer burden in lung transplant recipients. In our population-based study of recipients who were at least 1 year post-transplant, we found that standard incidence rates based on first SCC (or BCC) only, rose dramatically when multiplicity of new skin cancers were accounted for. This was especially true of SCC tumour incidence that reached a peak of 447 per 1000 lung transplant recipients per year, compared with 201 per 1000 PYs counting only the first SCC. Such high incident skin tumour rates are unprecedented and represent one of the heaviest skin cancer burdens reported in a defined population. Moreover, these tend to be aggressive SCCs with over half of these tumours invading the reticular dermis or beyond (where depth of invasion information was available). Compared with the estimated tumour incidence rates in the general Queensland population, the SCC tumour incidence rate in Queensland lung transplant recipients is 77 times higher and the BCC tumour incidence is 18 times higher.[14]

While other studies of skin cancer in lung transplant recipients have also shown substantial increases in risk relative to the general population, none have measured skin cancer multiplicity in lung transplant recipients. As mentioned above, many studies counted only the first skin cancer per year and some did not count SCCs and BCCs separately.[1–3,5] Others combined lung transplant recipients with heart transplant recipients,[1] and several assessed only the cumulative incidence of developing a skin cancer in a given period after transplantation.[4]

Commonly reported risk factors for developing keratinocyte cancer after organ transplantation are male sex, increasing age, high sunlight exposure and duration of immunosuppression.[13] Risk factors for a first skin cancer after lung transplantation at the Mayo Clinic[4] and in a Sydney hospital[5] were similar, and we have shown that of these risk factors, by far the strongest predictors of multiple SCCs or BCCs in lung transplant recipients are previous history of skin cancer and being aged ≥ 60 years. These are also the major predictive factors of multiple skin cancers in the general population.[14,15] In addition, ever having received treatment with voriconazole was associated with a doubling of SCC (but not BCC) tumour burden, and there was a suggestive dose–response effect, with ≥ 4 months of treatment increasing the risk more than fourfold. This finding is consistent with evidence from a systematic review of relevant studies published before September 2017, showing that lung transplant recipients and haematopoietic cell transplant recipients who had been treated with voriconazole had a doubling of risk of SCC but not of BCC, and that SCC risk increased with duration of voriconazole treatment.[11] Voriconazole is believed to enhance skin carcinogenesis through its

Table 3 Risk of developing multiple squamous cell carcinoma (SCC) and risk of developing multiple basal cell carcinoma (BCC) during follow-up of 125 lung transplant patients according to their baseline characteristics

Baseline characteristics	All N = 125	Patients with multiple SCC		Patients with multiple BCC	
		n (%)	IRR[a] (95% CI)	n (%)	IRR[a] (95% CI)
Age group, years					
< 60	90	10 (11)	Reference	16 (18)	Reference
≥ 60	35	19 (54)	6·6 (2·9–15·2)	14 (40)	3·1 (1·3–7·7)
Sex					
Female	53	7 (13)	Reference	7 (13)	Reference
Male	72	22 (31)	2·4 (0·9–6·1)	23 (32)	2·2 (0·8–6·2)
Completed education[a]					
Grade 12 or less	57	17 (30)	Reference	16 (28)	Reference
Trade/diploma	32	4 (13)	1·0 (0·3–3·0)	6 (19)	0·6 (0·2–1·8)
University/college	28	7 (25)	0·5 (0·2–1·6)	5 (18)	0·8 (0·3–2·4)
Natural skin colour					
Olive/medium	46	8 (17)	Reference	13 (28)	Reference
Fair	79	21 (27)	1·5 (0·6–3·6)	17 (22)	0·5 (0·2–1·4)
Lifetime painful sunburns[a]					
Up to five times	57	11 (19)	Reference	9 (16)	Reference
More than five times	60	17 (28)	0·9 (0·4–2·3)	18 (30)	1·9 (0·7–4·8)
Occupational sun exposure[a]					
Mainly indoors	60	10 (17)	Reference	10 (17)	Reference
Both indoors and outdoors/mainly outdoors	57	18 (32)	1·2 (0·5–3·0)	17 (30)	1·5(0·5–4·1)
Solar elastosis of neck					
None/little	72	7 (10)	Reference	13 (18)	Reference
Moderate/high	53	22 (42)	2·2 (0·8–5·9)	17 (32)	0·6 (0·2–1·5)
Skin cancers prior to transplant[a]					
No	87	18 (21)	Reference	19 (22)	Reference
Yes	17	7 (41)	1·4 (0·5–4·0)	6 (35)	1·1 (0·3–3·8)
Skin cancer history at baseline[a]					
No	47	2 (4)	Reference	2 (4)	Reference
Yes	70	27 (39)	6·9 (2·0–23·9)	25 (36)	10·5 (2·2–51·7)
Frequency of skin checks[a]					
≤ Once a year	70	12 (17)	Reference	12(17)	Reference
> Once a year	47	16 (34)	1·5 (0·6–3·6)	15 (32)	2·1 (0·8–5·3)
Number of usual sun protection measures used for sun exposure[a]					
< 2	48	11 (23)	Reference	8 (17)	Reference
≥ 2	69	17 (25)	1·5 (0·6–3·7)	19 (28)	0·9 (0·4–2·1)
Years immunosuppressed					
1–5	73	18 (25)	Reference	20 (27)	Reference
> 5	52	11 (21)	1·3 (0·5–3·0)	10 (19)	0·8 (0·3–2·1)
Voriconazole use					
No	43	9 (21)	Reference	13 (30)	Reference
Voriconazole < 4 months	44	10 (23)	1·9 (0·6–5·4)	11 (25)	1·9 (0·7–5·7)
Voriconazole ≥ 4 months	38	10 (26)	4·5 (1·3–15·3)	6 (16)	1·1 (0·4–3·7)

IRRs, incidence rate ratios. [a]IRR for multiple SCC (or BCC) adjusted for age, sex and skin cancer history at baseline.

photosensitizing properties.[16] In general, there is increasing reluctance among physicians to prescribe voriconazole, especially for patients with fair skin and/or previous skin cancer, as seen in our study where substantially fewer patients with a past history of skin cancer (58%) were prescribed voriconazole than those with no previous skin cancer (68%).

Our study was somewhat limited by the relatively short follow-up period ranging from 1 year to approximately 3·5 years, but our incidence estimates were age-adjusted and sufficiently robust to reveal their extraordinary magnitude. The severity of the SCC and BCC tumour burdens reflects not only the heavy immunosuppressant regimen that lung transplant recipients receive,[13] but also the high annual sun exposure that Queensland residents experience year-round.[17] Strengths of our study were its novelty in quantifying this annual skin cancer tumour burden and, moreover, the fact that it was carried out in a population-based cohort rather than a clinic-based cohort of lung transplant recipients. We had the ability to distinguish multiple SCCs and BCCs through annual skin examinations and intensive follow-up

of interim skin cancers, all of which were confirmed by histopathology.

The implications of multiplicity of SCCs and BCCs among lung transplant recipients, especially for those who experience high sun exposure, are far-reaching. The most pressing need is for prompt and adequate treatment of high volumes of skin cancers, especially new SCCs, as they arise in individual patients. We have recently reported on a high-throughput skin cancer clinic operating as a 'one-stop shop' dedicated to treating organ transplant recipients severely affected by skin cancers.[18,19] Close surveillance is required for lung transplant recipients, in particular those aged > 60 years with a history of skin cancer, or those treated with voriconazole. Finally, preventive measures are also very important and are more likely to be adopted if encouraged by medical personnel caring for and treating high-risk transplant recipients.[20,21]

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