Extreme Incidence of Skin Cancer in Kidney and Liver Transplant Recipients Living with High Sun Exposure

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Skin cancer is a major cause of morbidity and mortality in organ transplant recipients (OTRs) but accurate data about the extent of the problem are lacking. Cutaneous squamous cell carcinoma (SCC) causes the greatest burden with estimated incidence in European OTRs 60 to 200 times the general population rates (1, 2). Causes include immunosuppression and solar ultraviolet (UV) radiation, but oncogenic viruses and carcinogenic drugs may also contribute (3).

Most studies report cumulative incidence and are not transplant organ-specific. Annual incidence rates of SCC and basal cell carcinoma (BCC) in kidney transplant recipients have been published, but none in liver recipients (4–7). Furthermore, previous studies have failed to assess multiple skin cancers, though this is crucial for evaluating true skin cancer burdens for health service planning. This is especially true in countries like Australia with high skin cancer rates but no standard surveillance programs for OTRs (8–10). We therefore prospectively measured incidence rates of SCC and BCC in high-risk kidney and liver transplant recipients in Queensland.

The Skin Tumors in Allograft Recipients (STAR) study cohort comprised adult (≥18 years) high-risk, single-organ kidney and liver transplant recipients recruited at Princess Alexandra Hospital, 2012–2014. High-risk OTRs were defined as (*i*) white-skinned and (*ii*) either aged ≥40 years, immunosuppressed ≥10 years, or having previous skin cancer or actinic keratosis (AK). Focus on this high-risk group allowed characterization of OTRs who develop the bulk of skin cancers. OTRs newly receiving systemic retinoid or topical treatments and those with major co-morbidity were excluded. The study had ethical approval; all participants provided written informed consent. At recruitment, participants completed questionnaires providing demographic information and histories of sun exposure, treated skin cancer, skin examination frequency and sun protection (clothing, sunscreen). OTRs underwent full skin examinations by trained physicians who recorded skin colour, AKs and skin lesions on a body map, referring patients with suspicious lesions for management (11). Prevalent tumours identified at baseline (11) were excluded from analyses. Full skin examinations were repeated annually, to mid-2016. To ensure documentation of all new skin cancers, several methods were employed: quarterly telephone calls to participants about recent treatment; 'treatment cards' for physicians to record skin cancer diagnoses; regular review of public and private pathology databases.

Baseline characteristics were compared using Pearson's chi-squared test. Keratinocyte cancers (KC) included SCC, BCC and intraepidermal carcinoma (IEC). Organ-specific person-based IRs/1,000 person-year (py) were determined by the first SCC or BCC during follow-up. To account for multiple skin cancers per person we calculated tumour-based incidence of cancers as total number of SCCs [or BCCs]/total time in study. IRs were calculated as crude rates and also age-standardized to the 2001 Australian Population. To identify risk factors for multiple SCCs and KCs, we used negative binomial regression with offset to calculate incidence rate ratios (IRRs) and 95% CIs, adjusted for age and sex. Variables that defined high-risk OTRs were excluded in multivariable analyses. Analyses were performed using SAS 9.4.

Of 458 kidney and 276 liver transplant recipients who were eligible, 289 kidney (63%) and 205 liver (74%) transplant recipients were recruited. Main reasons for declining were difficulty attending study clinics (due to distance/time), or already having skin cancer monitoring by physician. Thirteen (3%) did not have baseline examination and 5 (1%) were lost to follow-up, resulting in 476 OTRs (281 kidney, 195 liver) analysed. Total follow-up varied by organ: 637 py for kidney and 475 py for liver recipients (3–36 months) (see Table SI[1] for baseline characteristics).

During follow-up, 265 OTRs developed 2,575 KCs (523 BCCs, 701 SCCs and 1351 IECs). Kidney recipients had higher age-standardized SCC IRs (119 and 309/1,000 py, person- and tumour-based respectively) than liver recipients (corresponding IRs, 79 and 206/1,000 py) (**Table I**), similarly for BCC. Seven OTRs (3 kidney, 4 liver) developed melanoma and two, Merkel cell carcinoma. Two Kaposi sarcomas, one sebaceous carcinoma, one atypical fibroxanthoma occurred in 4 kidney recipients.

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Table I. Crude and age-standardized incidence rates (95% CI) of skin cancer by transplant organ type as persons affected or total numbers of tumors

	Kidney transplant recipients ($n = 281$)	Liver transplant recipients ($n = 195$)
Crude incidence rates, persons affected, per 1,000 person-years		
Squamous cell carcinoma	173 (143–208)	112 (85–146)
Basal cell carcinoma	143 (118–175)	89 (66–121)
Age-standardized incidence rates, persons affected, per 1,000 person-years		
Squamous cell carcinoma	119 (91–146)	79 (38–120)
Basal cell carcinoma	88 (67–109)	79 (38–120)
Crude incidence rates, total numbers of tumors, per 1,000 person-years		
Squamous cell carcinoma	577 (528–630)	379 (331–434)
Basal cell carcinoma	470 (427–519)	221 (185–264)
Age-standardized incidence rates, total numbers of tumors, per 1,000 person-years		
Squamous cell carcinoma	309 (275–343)	206 (152–261)
Basal cell carcinoma	253 (224–282)	121 (84–158)

Being older (≥60), male, Australian-born, not college-educated, and having fair skin and skin checks >1/year were the main factors associated with first study SCC, KC and cancer multiplicity (Table SII[1]).

We have shown that kidney and liver transplant recipients with past actinic lesions, aged ≥40 years or immunosuppressed ≥10 years, residing in sunny climates carry extreme skin cancer incidence rates. Most evidence to date relies on cumulative incidence in kidney transplant recipients, though a study of annual incidence in selected Queensland kidney transplant recipients more than 15 years ago reported crude rates similar to ours (7). Even allowing for our focus on high-risk patients, differences between these past (7) and present studies in Queensland and studies from higher latitudes are stark. For example, SCC incidence rates reported in UK OTRs of broadly similar genetic stock, varied from 35 to 71/1,000 py (4, 6), an order of magnitude lower than corresponding Queensland rates. UV-induced genetic mutations in the p53 gene, NOTCH1 and FGFR3 combine with immunosuppressive factors to reduce immune surveillance (12, 13). The higher skin cancer risk in kidney than liver transplant recipients is consistent with higher levels of immunosuppression in the former.

We found similar risk factors for KC as other studies (14). OTRs having more frequent skin checks especially those with previous KC, had greater risk of KC reflecting their higher surveillance. Those with tertiary education had half the risk of multiple KCs of those with high school education. Study strengths were the multiple strategies for skin cancer capture, and minimal losses to follow-up. We calculated separate SCC and BCC organ-specific annual incidence rates (not cumulative), and provided new knowledge about rates of SCC and BCC multiplicity. We restricted the study to 476 high-risk OTRs who comprised 42% of all OTRs at the transplantation hospital, so we cannot generalize these results to all kidney and liver recipients. A proportion declined enrolment due to ongoing dermatologic care, which may have caused underestimation of incidence.

The extreme skin cancer incidence rates reported here reveal the substantial extra burden among OTRs caused by high sun exposure. They highlight the need for specialized, dedicated surveillance clinics to ensure rapid skin cancer treatment and regular prevention education by clinical staff (15).

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