Actinic keratosis-related signs predictive of squamous cell carcinoma in renal transplant recipients: a nested case-control study

Running title: Predicting malignancy in actinically damaged skin

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What's already known about this topic?

- Squamous cell carcinoma (SCC) commonly arises in actinically damaged skin.

- Intraepidermal carcinoma (IEC) is a precursor of SCC that usually develops on sun exposed skin.

- Actinic keratoses (AKs) are associated with an increased risk of SCC.

- Actinic field change represents keratinocytes with UV-specific pre-cancerous genetic mutations.

What does this study add?

- Certain features of actinic damage on pre-defined areas of skin on the head, neck and upper limbs can predict short-medium term SCC or IEC risk.

- The presence of AK that affects greater than $1cm^2$ skin (AK patch) on a pre-defined site significantly increases risk of SCC or IEC within 18 months.

- The number of AKs and the percentage of area affected by AKs are also associated with an increased risk of SCC or IEC.

ABSTRACT

Background: Squamous cell carcinoma (SCC) and intraepidermal carcinoma (IEC) commonly arise in actinically damaged skin.

Objective: To identify clinical features of actinic change that correlate with an increased risk of SCC or IEC in the short-medium term as guidance for prioritising field treatment.

Methods: In a nested case-control study, cases were renal transplant recipients (RTRs) who developed an incident SCC or IEC within 18 months following baseline examination and photography. Controls without SCC/IEC were matched to cases on age, sex and duration of immunosuppression. Pre-defined skin sites on head, neck and upper limbs were examined using baseline photographs to objectively assess the following features of actinic damage: presence of actinic keratosis (AK) patch (defined as AK $>1cm^2$), number of AK patches, number of AKs and area affected by AK. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using McNemar's test to identify differences in SCC/IEC risk combined and SCC risk alone between case and control skin sites.

Results: 39 cases were matched to 39 controls. Significant associations with the presence of an AK patch, number of AK patches, number of AKs and area affected by AKs were identified. The presence of an AK patch conferred an 18-fold increased risk of SCC (OR

18.00, 95% CI 2.84-750) and a 7-fold increased risk of SCC/IEC combined (OR 6.6, 95% CI 2.56-21.66).

Conclusion: AK patches are predictive of SCC/IEC development within 18 months. This can be used to guide site selection for field treatment in patients with widespread actinic damage.

INTRODUCTION

Cutaneous squamous cell carcinoma (SCC) is a malignant tumour of epidermal keratinocytes that usually arises on body sites with high sun exposure. [1,2] Ultraviolet (UV) radiation is recognised as a principal cause with epidemiological studies showing a significant association with occupational sun exposure and cumulative sun exposure. [3,4] Intraepidermal carcinoma (IEC) also arises on sun-exposed sites and is often associated with SCC. [5-7] Mutations in the p53 oncogene are commonly detected in IEC and SCC, suggesting that dysregulation of p53 pathways is a key event in SCC carcinogenesis. [8] Furthermore, UV radiation has been identified as a cause of p53 mutations in keratinocytes. [9]

Actinic keratoses (AKs) are intraepithelial dysplastic keratinocytic lesions which are diagnosed clinically as scaly erythematous papules or plaques. They frequently arise on heavily sun-exposed sites as a recognised consequence of chronic UV damage. [10,11] AKs are a strong risk factor for SCC, both in the general population and in immunosuppressed transplant recipients. [12,13] A recent study has shown that the presence of large confluent AKs ($>1cm^2$) is an additional risk factor for SCC in transplant recipients. [14]

The evidence, therefore, corroborates the view that SCC and IEC primarily occur in actinically damaged skin that has undergone genetic mutation, supporting the notion of 'field change' in the genesis of cutaneous SCC. [15,16] Specifically, field change has been histopathologically defined as an area consisting of abnormal epithelial cells, which do not show invasive growth or metastatic behaviour. [17] These areas likely represent the first stages

of carcinogenesis and although it is recommended to treat actinic field change, there is insufficient evidence to establish a working clinical definition of what constitutes field change.[18-21] Developing such a definition is clinically important to enable the identification and treatment of areas of skin that carry the greatest risk of malignancy, particularly in patients with widespread actinic damage.

Therefore the aim of this study was to identify precise clinical parameters for actinic damage which can be used to predict the short- to medium-term risk of SCC or IEC on pre-defined areas of sun-exposed skin and to facilitate selection of skin sites with priority for field treatment.

METHODS

Study design

A nested, anatomic site-specific, case-control study was conducted among participants of the Skin Tumours in Allograft Recipients (STAR) cohort. STAR is a prospective study whose primary aim is to assess the skin cancer burden and associated factors in organ transplant recipients (OTRs) in subtropical Queensland. White-skinned Caucasian OTRs were eligible for inclusion if they were aged 18 years and over, at least one year post-transplant with stable immunosuppression and had a history of skin cancer or AK, or if no such history, were aged 40 years or older or had received at least 10 years of immunosuppressive therapy. OTRs were excluded if there was a history of recent topical field treatment (< 6 months) or if they were receiving oral retinoid therapy (unless on a stable dose for > 6 months). The study received approval from relevant institutional ethics committees and participants provided written informed consent.

All participants received a detailed baseline skin examination by a trained physician. Participants were subsequently examined at 12-monthly intervals at study clinics, with three-

monthly telephone interviews to ensure all interim skin cancers between annual study skin examinations were identified. All skin tumours suspected of malignancy at study clinics and all self-reported skin cancers were histopathologically confirmed.

Cases were study RTRs who developed an incident SCC or IEC on the face, forearms or hands within 18 months of baseline skin examination. Controls were defined as RTRs who did not develop SCC or IEC on the pre-defined study subsites face, forearms or hands within 18 months of the baseline skin examination (given this was a priori a site-specific study, controls may have developed SCC/IEC on non-study sites without violating the study protocol).

Cases and controls were matched 1:1 on sex, age (± 5 years) and time since first transplantation (± 5 years), the latter representing duration of immunosuppression. In addition, cases were matched to controls on the basis of pre-defined skin sites, namely seven facial sites and four upper limb sites, including exact matching on laterality. Pre-defined skin sites were chosen for the present study of clinical features of actinic damage according to ease and feasibility of treating the entire area. In total, 11 skin sites that were potentially treatable topically were examined: left and right upper face (demarcated by the normal hairline, the upper eyebrow edge, the midline of the face and a line from the lateral canthus to the tragus of the ear), left and right lower face (demarcated by a line from the lateral canthus to the ear, the lower eyebrow edge, the midline of the face, outermost edge of nasal sidewall and the edge of the jaw), nose, left and right ear, left and right dorsal forearm (demarcated by the wrist and elbow crease) and left and right dorsal hand (Fig. 1).

If multiple skin sites were examined per participant, these were each matched to an identical skin site in the control participant. In instances where SCC and IEC had developed on the same skin site, only one outcome of either SCC alone or SCC/IEC combined was analysed.

Data collection

Standardised high quality digital photographs were taken of the face, forearms and hands of RTRs at baseline using a Canon DS126271 digital camera with Macro Lens EF-S 60mm 1:2:8 USM (Tokyo, Japan), photo-studio flash lighting, a soft-box and white screen.

The baseline digital photographs of identified case and control skin sites were subsequently examined by a dermatology-trained physician to identify the following features of actinic damage: the presence of an AK patch (defined as an AK greater than $1cm^2$), the number of AK patches and the number of AKs. Additionally the percentages of the defined areas affected by AK, erythema and pigment change (hypo- and hyperpigmentation) were assessed and recorded as 0%, 1-25%, >25-50%, >50%-75% or >75%. All assessments of digital photographs of participants' skin were conducted blinded to the case/control status of the participants. AK was identified on photographs as a scaly erythematous papule or plaque.[16]

Statistical analysis

Baseline characteristics of cases and controls were summarised and differences between matched pairs tested for significance using paired t-test. Potential explanatory variables were dichotomised and McNemar's test was applied to identify features of actinic damage significantly associated with the two outcomes of developing a) either SCC or IEC and b) SCC alone. Odds ratios and 95% confidence intervals (CIs) were calculated as the measure of association. Kendall's tau-b test was used to assess the correlation between AK counts on photographs versus clinical examination in a random selection of 30 skin sites. A *P* value of 0.05 or less was considered significant. All analyses were performed using SPSS v21 (Armonk, NY: IBM Corp).

RESULTS

Of 59 cases and 95 controls that fulfilled inclusion criteria, 39 cases with complete high quality photographs were successfully matched to 39 controls. Of the 39 matched pairs, 26 were male. Ages ranged from 32 to 75 years and mean age of cases (58 ± 9 years) and controls (57 ± 9 years) were very similar. Duration of immunosuppression ranged from 1 to 25 years with mean 9 (± 7) years for cases and controls. The overall differences between matched pairs were -0.9 years for age and -0.3 years for duration of immunosuppression.

69 matched skin sites were evaluated in total, as 14 case participants developed SCC or IEC on multiple skin sites and six skin sites developed both SCC and IEC and therefore these were analysed as one for the outcome of SCC/IEC combined (Table 1). Of the 69 matched skin sites, a new SCC developed on 27 case skin sites and an IEC occurred on 48 overlapping case skin sites in the 18 months follow-up period (Table 1; Fig. 1). Twenty of the 27 SCCs showed moderate differentiation, three were poorly differentiated and four were well differentiated; only one SCC was greater than 2cm in diameter. The left lower face was the skin site with the highest number of new SCC and IEC lesions in the study period.

SCC/IEC combined

An AK patch was present on 58% of case skin sites at baseline that developed either SCC or IEC in the following 18 months but on only 17% of control skin sites at baseline (Table 2). The number of AK patches ranged from 0-6 in control skin sites (median 0) and 0-13 in case sites (median 1). The presence of an AK patch significantly increased the risk of either SCC or IEC by more than 6-fold (OR 6.6, 95% CI 2.56-21.66). Skin sites with three or more AK patches also had a significantly increased risk of either SCC or IEC when compared with sites with less than three AK patches (OR 5.68, 95% CI 1.64-30.18). The total number of AKs per site ranged from 0-49 in all participants and only 16% of case skin sites had 0

AKs compared with 45% of control skin sites. Furthermore, the majority of case skin sites had three or more AKs (64%) whilst only 22% of control skin sites had this feature, corresponding to a more than 4-fold increase in risk of either SCC or IEC (OR 4.63, 95% CI 2.12-11.45). 23% of case skin sites had AKs involving 25% or more of the area compared with only 4% of control skin sites and this was statistically significant (OR 5.33, 95% CI, 1.53-28.56). There was no significant difference in area affected by erythema or pigmentation change between case and control sites (*P* value 0.15 and 0.58, respectively).

SCC alone

With regards to the SCC only outcome, variation between case and control sites was more pronounced. The vast majority of case skin sites with incident SCC (78%) had an AK patch present at baseline, compared with only 15% of control skin sites and risk of SCC was increased by almost 20-fold (OR 18.00, 95% CI 2.84-750). There were three or more AK patches on 10 case skin sites (37%) versus only one control skin site (4%). There was also a notable difference in the number of AKs with the majority of case skin sites (82%) having three or more AKs compared with only 15% of control skin sites. No control skin sites had >25% of the area involving AKs, whereas this was true in 41% of skin sites that later developed SCC. Further analysis could not be performed for the variables 'number of AK patches', 'number of AKs' and 'percentage of area involving AK' due to lack of sufficient discordant matched pairs. There was no significant difference in area affected by erythema or pigment change between case and control sites (*P* > 0.05).

Consistency of photographic and clinical assessment of AKs

Consistency of assessing baseline AK counts using digital photographs compared with clinical examination (as recorded by examining physicians at baseline on standard body-

charts) was evaluated in a random selection of 30 skin sites examined. Given that AK counts vary considerably in clinical examinations between physicians [22,23] and that tactile information is absent in photographic assessment, a tolerance of ± 1 AK was set for the comparison between photographs and clinical examination. Using this method, AK counts from photographs were consistent with AK counts at baseline clinical examination for 25 of the 30 (83%) randomly evaluated pre-defined sites on the head and neck (Kendall's tau-b correlation coefficient = 0.78, P <0.001).

DISCUSSION

It is widely accepted that actinic damage is a risk factor for SCC in both the general and immunosuppressed populations. [24-26] However, because AKs are so prevalent in exposed skin with severe actinic damage, identifying confined anatomic skin sites at high risk of developing SCC or IEC is essential to enable targeted treatment. Our study is novel in its examination of pre-defined skin sites because of the practicability for targeted treatment and in its establishing high risk of either SCC or IEC in the short-medium term (18 months). Furthermore, this is the first study to explore the relevance of an AK patch in localised, pre-defined areas of skin.

We showed that a defined skin site with an AK greater than $1cm^2$ (AK patch) is approximately seven times more likely to develop either SCC or IEC than sites without this feature. Furthermore, skin sites with an AK patch present had an almost 20-fold increased risk of SCC, when compared with skin sites without this feature (95% CI 2.84-750) (the wide confidence interval reflecting the small numbers of discordant pairs in the assessment of SCC risk). The number of AK patches was also associated with an increased risk with sites having three or more AK patches being six times more likely to develop either SCC or IEC within an 18 month period than those with less than three AK patches. This may be an

underestimation, however, as only 22 skin sites had three or more AK patches present. Skin sites with three or more AKs or AKs covering 25% or more of the total area of the field had a five-fold increased risk of either SCC or IEC compared with sites with less than 25% area affected.

Risk estimates for SCC alone could not be calculated because of zero cell numbers in the discordant combination of low for cases and high for controls for the variables number of AK patches, number of AKs and percentage area involving AK. This discordance in itself highlights the significant disparity between actinic damage in case and control sites and illustrates the dramatic effect these factors have on SCC risk. The percentage of area affected by erythema and pigmentation change did not vary significantly between case and control sites for either outcome of SCC/IEC combined or SCC alone.

Previous studies have quantified the risk of AK progression to SCC with the hope of directing management towards either active treatment or a 'watch and wait' approach. The risk estimations for progression to SCC have varied between 0-0.53% per year, leaving clinicians with differing opinions on the cost-benefit result of treating AKs. [13,27] Our study therefore provides important evidence required to guide the management of actinically damaged skin and hence to create a new practical clinical working definition of actinic field change by exploring the concept of AK patch, which could guide clinicians to a staggered approach for field-directed treatment.

We recognise that this study is limited by the small numbers of cases, particularly SCC, where a larger sample would have improved risk estimation. Our study was underpowered and a larger study may be required to confirm that AK patches are independently predictive of SCC/IEC development. Additionally, although we examined 11 pre-defined skin sites, the various facial and upper limb skin sites were not of equal size. Furthermore, using two or more assessors to extract the photography data would have

enabled a comparison and assessment of inter-observer reliability. High-quality digital photographs (as opposed to advanced imaging techniques) were used as reasonable surrogates for clinical examination, which in practice does not allow painstaking assessment of details of actinic damage such as surface area affected. There was high positive correlation between AK counts using photography and on clinical examination, thereby supporting the consistency of our method of using photography for the assessment of actinic damage. Moreover, the blind assessment of the photographs ensured that any significant variations in results between case and control sites cannot be explained on the basis of bias or technique alone. Therefore, although photography was used, we believe the results of this study can be extrapolated to the clinical setting with significant features guiding site selection and treatment. Additionally despite only examining RTRs, studies have shown that keratinocyte cancers in RTRs and the general population share very similar risk factors and likely a similar aetiology. [1,25] We therefore believe that the results of this study are generalizable to immunocompetent patients, although skin cancers in the latter are likely to develop in the longer term rather than within an 18 month period as observed here in RTRs.

In conclusion, this study has identified clinical risk factors on pre-defined skin sites that can be used as predictors for malignancy in the short to medium term. Field-directed treatment such as the use of topical agents, photodynamic or laser therapy, aimed at high-risk sites with features such as the presence of an AK patch can be employed, particularly in patients with widespread actinic damage to reduce future SCC/IEC risk. Further research directed at site-specific analysis is required to better understand site-specific risk factors and prioritise field-directed treatment in individuals with a high degree of UV damage.

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Table 1. Location of incident squamous cell carcinoma (SCC), intraepidermal carcinoma

(IEC) and numbers of actinic keratoses (AKs) and AK patches on case skin sites

Skin site	Number of cases with SCCs n (%)	Number of cases with IECs n (%)	Total IEC/SCC n (%)	Total number of AKs n (%)	Total number of AK patches n (%)
Left upper face	2 (7)	4 (8)	6 (8)	26 (8)	11 (9)
Right upper face	4 (15)	7 (15)	11 (15)	41 (12)	21 (17)
Left ear	3 (11)	2 (4)	5 (7)	7 (2)	4 (3)
Right ear	0 (0)	2 (4)	2 (3)	6 (2)	3 (2)
Left lower face	4 (15)	10 (21)	14 (19)	50 (15)	20 (17)
Right lower face	2 (7)	3 (6)	5 (7)	29 (8)	9 (7)
Left forearm	3 (11)	5 (10)	8 (11)	36 (11)	7 (6)
Right forearm	2 (7)	4 (8)	6 (8)	70 (20)	14 (12)
Left hand	2 (7)	4 (8)	6 (8)	23 (7)	3 (2)
Right hand	4 (15)	4 (8)	8 (11)	47 (14)	25 (21)
Nose	1 (4)	3 (6)	4 (5)	5 (1)	4 (3)
Total	27 (100)	48 (100)	75 (100)[*]	340 (100)	121 (100)

* Only 69 case skin sites examined in total, as 6 sites which developed both SCC and IEC were

analysed as one for the outcome of either SCC or IEC.

Table 2. Summary of differences between case and control skin sites with calculated odds

ratios (ORs) and 95% confidence intervals (CI)

Variable		SCC/IEC combined				SCC alone			
		Case skin sites n (%)	Control skin sites n (%)	Odds ratio (95% CI)	*P* value	Case skin sites n (%)	Control skin sites n (%)	Odds ratio (95% CI)	*P* value
Presence of actinic keratosis patch	No Yes	29 (42) 40 (58)	57 (83) 12 (17)	6.60 (2.56-21.66)	<0.001	6 (22) 21 (78)	23 (85) 4 (15)	18.00 (2.84-750)	<0.001
No. actinic keratosis patches	0-2 3+	51 (74) 18 (26)	65 (94) 4 (6)	5.68 (1.64-30.18)	0.004	17 (63) 10 (37)	26 (96) 1 (4)	*	<0.001
No. actinic keratosis	0 -2 3+	25 (36) 44 (64)	54 (78) 15 (22)	4.63 (2.12-11.45)	<0.001	5 (18) 22 (82)	23 (85) 4 (15)	*	<0.001
Percentage of area involving actinic keratosis	<25% >25%	53 (77) 16 (23)	66 (96) 3 (4)	5.33 (1.53-28.56)	0.006	16 (59) 11 (41)	27 (100) 0 (0)	*	0.014
Percentage of area involving erythema	<25% >25%	49 (71) 20 (29)	57 (83) 12 (17)	2.00 (0.81-5.40)	0.15	19 (70) 8 (30)	20 (74) 7 (26)	1.17 (0.34-4.2)	0.88
Percentage of area involving pigmentation change	<25% >25%	54 (78) 15 (22)	51 (74) 18 (26)	1.6 (0.46-6.22)	0.58	20 (74) 7 (26)	21 (78) 6 (22)	1.50 (0.17-17.96)	0.65

* Incalculable due to lack of discordance within matched pairs.

Figure 1. Demarcation of selected facial and upper limb skin sites