

Inflammatory Dietary Patterns and Risk of Keratinocyte Cancers in Kidney Transplant Recipients: Prospective Cohort Study

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Keywords

Kidney transplantation · Keratinocyte cancer · Inflammatory diet · Squamous cell carcinoma · Basal cell carcinoma

Abstract

Background: Kidney transplant recipients (KTRs) are at increased risk of cutaneous squamous (SCC) and basal cell carcinomas (BCC) due to immunosuppression and sun exposure. Skin carcinogenesis involves inflammation, and foods that promote inflammation may promote carcinogenesis.

Methods: We prospectively examined the association between pro-inflammatory diets and SCC and BCC incidence in KTRs in Queensland, Australia. We recruited KTRs at high risk of skin cancer (aged ≥ 18 years and previously affected; or aged ≥ 40 ; or immunosuppressed ≥ 10 years) between 2012 and 2014 and followed up until June 2016. A baseline dietary questionnaire was used to calculate modified-Empirical Dietary Inflammatory Pattern (EDIP) scores to indicate dietary inflammatory capacity; higher scores indicated pro-inflammatory diets. EDIP scores were ranked into 3 groups. Outcomes were histologically confirmed SCC and BCC. Adjusted relative risks (RR_{adj}) and 95% CIs were estimated using negative binomial regression. **Results:** Among 260 KTRs, 100

(38%) and 93 (36%) developed at least 1 new SCC and BCC, with 426 SCC and 343 BCC diagnosed in the follow-up period. The highest modified-EDIP score group (vs. lowest) were at increased risk of SCC (RR_{adj} 1.79, 95% CI 1.01–3.16) but not BCC. Pro-inflammatory diets may increase SCC but not BCC risk among KTRs. **Conclusions:** Inflammatory diets may increase the risk of SCC in KTRs.

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Introduction

Kidney transplant recipients (KTRs) are at increased risk of keratinocyte cancer, namely squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) [1]. This is due to the intense immunosuppression required to prevent allograft rejection, compounding the background carcinogenic effects of ultraviolet (UV) radiation exposure [1]. Improved transplant survival has led to these cancers becoming an increasingly important cause of morbidity and mortality in KTRs [1], with a reported 34-fold increase in SCC incidence [2] and a 27-fold increase in keratinocyte cancer mortality compared to the general population [3]. Current measures to decrease skin cancer

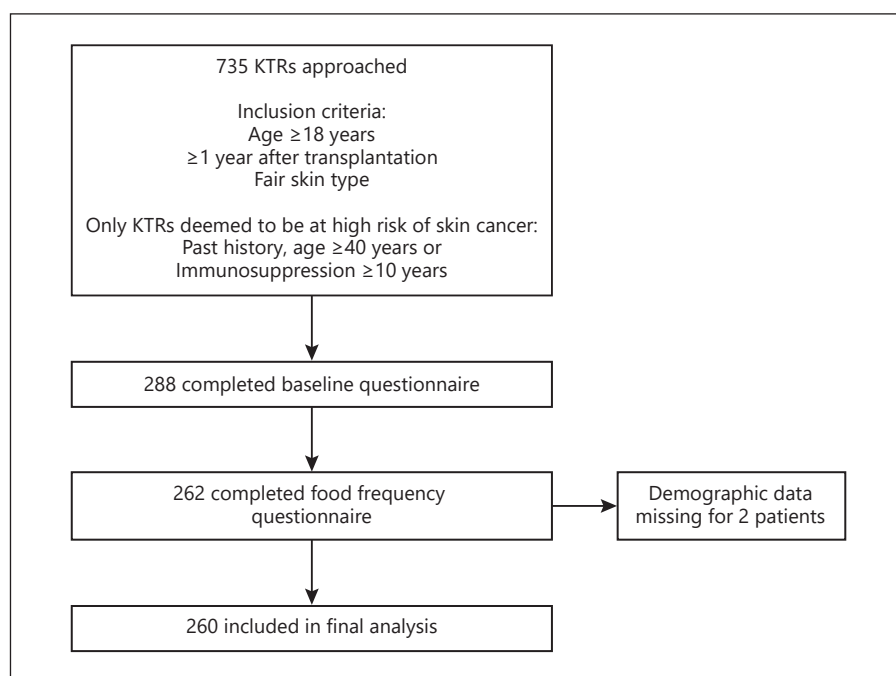


Fig. 1. Flowchart of Materials and Methods. KTRs, kidney transplant recipients.

in KTRs include emphasising sun protection [4], reducing immunosuppressant medication to the lowest effective dose [5], or prescribing acitretin or nicotinamide for systemic chemoprevention [6, 7]. Despite these measures, incidence rates in KTRs remain high, and adjunct preventive measures are urgently needed.

Dietary modification potentially provides one such adjunct preventive measure. Systemic inflammation enhances skin carcinogenesis and there is growing evidence for an association between diet and skin cancer through inflammatory pathways [8–10]. Individual food components such as a high proportionate ω -6 fatty acid to ω -3 fatty acid intake promote inflammatory pathways and can increase SCC risk [11, 12].

The Empirical Dietary Inflammatory Pattern (EDIP) score is a robust measure of the association between dietary patterns and inflammation [13]. Higher EDIP scores represent a weighted intake of food groups that were predictive of high levels of inflammatory markers, including TNF- α , CRP, IL-6, and adiponectin [13]. Developed in the United States using data from the Nurses' Health Study, the score was validated in 2 independent cohorts, and a high EDIP score has been associated with increased colorectal and ovarian cancer risk [14, 15]. No studies have investigated the inflammatory potential of dietary patterns and risk of skin cancer. We hypothesised that inflammatory dietary patterns using the EDIP

score are positively associated with skin cancer incidence in KTRs and tested this in a high-risk cohort in Australia.

Materials and Methods

For further details, see the online supplementary material (see www.karger.com/doi/10.1159/000509875 for all online suppl. material); Figure 1 [15–19].

Results

We approached 735 KTRs, and 288 (39%) agreed to participate and completed the baseline questionnaire. Among them, 262 recipients completed the food frequency questionnaire (FFQ), with 2 exclusions due to missing data for a total of 260 (90%) included in the study. The mean age of participants was 54 years (SD 11); 96 (37%) were female; and the median duration of immunosuppression was 9 years (range 1–42) and median follow-up was 3 years (range 0.2–3.6). Eight-two (32%) KTRs had never had a history of skin cancer excision, and 105 (40%) had skin checks more than annually (Table 1).

One hundred KTRs (38%) were affected by at least 1 new SCC, and 93 (36%) were affected by at least 1 new BCC in the follow-up period, with a total number of 426

Table 1. Characteristics of renal transplant recipients: low, intermediate, and high EDIP groups

	All (<i>n</i> = 260)	Low (<i>n</i> = 78)	Intermediate (<i>n</i> = 78)	High (<i>n</i> = 104)
Age (mean ± SD), years	54±11	53±11	55±12	54±11
Sex, females	96 (37)	28 (29)	29 (30)	39 (41)
Place of birth				
Australia	206 (79)	67 (86)	54 (69)	85 (82)
Outside Australia	55 (21)	11 (14)	24 (31)	19 (18)
Education				
High school	144 (55)	42 (54)	42 (58)	60 (58)
Trade, certificate, or diploma	64 (25)	16 (21)	22 (25)	26 (25)
University/college	52 (20)	20 (26)	14 (18)	18 (17)
Natural complexion				
Medium/olive	94 (36)	33 (42)	28 (36)	33 (32)
Fair	166 (64)	45 (58)	50 (64)	71 (68)
Smoking status				
Never smoker	139 (54)	43 (55)	37 (47)	59 (57)
Ever smoker				
Current smoker	9 (3)	2 (3)	4 (5)	3 (2)
Ex-smoker	112 (42)	33 (42)	37 (47)	42 (40)
Median immunosuppressed time (range), years	9 (1–42)	9 (1–37)	10 (1–38)	10 (1–42)
Past skin cancers excised				
Nil	82 (32)	24 (30)	27 (34)	31 (30)
≤5	107 (41)	35 (45)	32 (41)	40 (38)
6–10	26 (10)	10 (13)	7 (9)	9 (9)
>10	45 (17)	9 (12)	12 (15)	24 (23)
Frequency of skin checks				
Less frequent or equal to once a year	155 (60)	44 (56)	46 (59)	65 (63)
More than once a year	105 (40)	34 (44)	32 (41)	39 (38)
Median modified-EDIP score (range)	0.21 (0.08 to 1.03)	0.08 (–0.61 to 0.13)	0.18 (0.13 to 0.23)	0.33 (0.24 to 1.03)

n (%), unless indicated otherwise. EDIP, empirical dietary inflammatory pattern; SD, standard deviation.

new SCC and 343 new BCC patients. The tumour-based incidence was 533 and 429 per 1,000 person-years for SCC and BCC, respectively (online suppl. Table 1).

The median (range) for modified-EDIP scores was 0.21 (0.08–1.03; Table 1). The associations between ranked deciles of the modified-EDIP scores and new SCC were used to determine 2 cutoff points. While observed relative risks were unstable due to the small number of observations in each group, 3 groups were created according to what appeared to be cutoff points of changing relative risks (online suppl. Fig. 1). The first 3 deciles were combined into the lowest group which had 78 KTRs, deciles 4–6 were combined into the intermediate group with 78 KTRs, and deciles 7–10 were combined into the highest group with 104 KTRs. The median (range) modified-EDIP score of the 3 groups were 0.08 (–0.61 to 0.13), 0.18 (0.13–0.23), and 0.33 (0.24–1.03), respectively. Since we did not observe clear cutoff points for the EDIP scores and BCC, we used the same cutoff points as for SCC analysis (online suppl. Fig. 2).

Table 2. Modified-EDIP score and risk of SCC and BCC in renal transplant recipients (*n* = 260)

Modified-EDIP group	Relative risk (95% CI)	
	SCC	BCC
Base model ^a		
Low (<i>n</i> = 78)	1.00 (ref.)	1.00 (ref.)
Intermediate (<i>n</i> = 78)	1.75 (0.94–3.28)	1.52 (0.77–3.00)
High (<i>n</i> = 104)	2.56 (1.41–4.67)	1.52 (0.80–2.91)
Final model ^b		
Low (<i>n</i> = 78)	1.00 (ref.)	1.00 (ref.)
Intermediate (<i>n</i> = 78)	1.68 (0.93–3.04)	2.02 (1.13–3.61)
High (<i>n</i> = 104)	1.79 (1.01–3.16)	1.21 (0.69–2.14)

^a Base model: adjusted for age and sex for all tumour types. ^b Final model for BCC: age, sex, skin cancer excision history. Final model for SCC: age, sex, education, skin cancer excision history. BCC, basal cell carcinoma; EDIP, empirical dietary inflammatory pattern; SCC, squamous cell carcinoma.

The KTRs with the highest modified-EDIP scores, representing dietary patterns with the highest inflammatory potential, were at significantly increased risk of SCC compared to the low group (RR_{adj} 1.79, 95% CI 1.01–3.16). This was also true for the intermediate modified-EDIP group when compared to the lowest; however, the results were non-significant (RR_{adj} 1.68, 95% CI 0.93–3.04; Table 2). The higher modified-EDIP score groups were not associated with an increased BCC tumour risk when compared to the lowest group (low vs. intermediate RR_{adj} 1.32, 95% CI 0.67–2.59; low vs. high RR_{adj} 1.54, 95% CI 0.81–2.92; Table 2).

The results from person-based analyses were weaker when compared to tumour-based analyses. There was no significant association between higher modified-EDIP groups and person-based SCC (low vs. intermediate RR_{adj} 1.26, 95% CI 0.72–2.20; low vs. high RR_{adj} 1.21, 95% CI 0.69–2.12). The modified-EDIP was also not associated with person-based BCC risk, (low vs. intermediate RR_{adj} 1.44, 95% CI 0.84–2.46; low vs. high RR_{adj} 1.33, 95% CI 0.87–2.08) (online suppl. Table 2).

Discussion

We prospectively examined pro-inflammatory dietary patterns using modified-EDIP score and risk of multiple SCC and BCC among KTRs. A pro-inflammatory diet was associated with a significantly increased risk of multiple SCC but not BCC in KTRs. Tumour-based incidence endpoints were a more statistically powerful test of our hypothesis, and, as expected, person-based risks of SCC and BCC in relation to pro-inflammatory dietary patterns were similarly, but not significantly, increased.

A growing body of evidence suggests dietary intake can influence cancer development, including skin cancer [20]. Diets high in fat, meat, and dairy have been associated with pro-inflammatory biomarkers [21, 22], similar to those measured in EDIP [13]. High dairy intake and a dietary pattern high in meat and fat intake are associated with increased SCC risk [20, 23]. ω -6 fatty acids, found in meat, eggs, and vegetable oils, are pro-inflammatory [24], and high proportionate consumption of ω -6 fatty acids to ω -3 fatty acids has been associated with increased SCC risk [11]. Thus, the increased SCC risk in KTRs consuming a pro-inflammatory diet in this study is consistent with the observed association of diet on SCC risk in the immunocompetent population. While these findings support an association between diet and risk of SCC, this an observational study with relatively smaller numbers,

and causation cannot be implied. The findings regarding diet and BCC risk are also consistent with previous studies in the immunocompetent population that have found an increased risk for SCC but null results for BCC risk [20, 23]. The influence of diet on UV carcinogenesis is complex and seems to affect BCC to a lesser extent for reasons not fully understood.

There are limitations in the use of FFQs to measure dietary intake, including greater measurement error than using dietary records, for example [25, 26]. On the other hand, FFQs can capture long-term habitual diet and rank the levels of nutrient, food, or food group intakes [25, 26]. Furthermore, we measured usual intake in the previous 12 months only at baseline, and some KTRs may have changed their diet as a consequence of intervening comorbidities, though in general dietary habits are relatively stable over time in adults [27]. Regarding the EDIP score itself, we used a modified version, as our FFQ did not contain all components of the original EDIP score [13]. The original EDIP score evaluation noted other versions of the score with fewer components which were robust in associations with inflammatory biomarkers which may indicate that an association can be found with fewer food groups [13]. Furthermore, the EDIP score was created and validated in American health professionals, whose particular diets have given rise to some unexpected foods (such as pizza and beer) being classified as major anti-inflammatory components of the diet, notwithstanding potential biological mechanisms of action [28, 29].

Nonetheless, strengths of this study include the prospective collection of data with close follow-up of keratinocyte cancer outcomes with histopathological diagnosis and adjustment for important confounders. This is the first study to explore the association between dietary patterns and skin cancer among KTRs, and, if confirmed, the findings offer health professionals the potential additional strategy to advise their transplant patients who are at high risk of SCC to avoid pro-inflammatory diets.

Conclusion

A pro-inflammatory diet was significantly associated with an increased risk of SCC but not BCC development in KTRs. Further large prospective studies are required to confirm the possible beneficial effects of reducing a patients' dietary inflammatory potential on SCC risk in KTRs.

Key Message

An inflammatory diet may increase the risk of SCC in renal transplant recipients.

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Statement of Ethics

Ethical approval was obtained from the Metro South and QIMR Berghofer Human Research Ethics Committees. All participants provided written, informed consent.

Disclosure Statement

There are no conflicts of interest to declare.

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Author Contributions

E.S. participated in writing of the paper, performance of the research, and data analysis. A.C.G. participated in research design, writing of the paper, and data analysis. K.M. participated in research design, writing of the paper, performance of the research, and managing and analysing the data.

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