CLINICAL REPORT

Risk of Non-melanoma Skin Cancer in Patients with Chronic Kidney Disease and its Relationship to Uraemic Pruritus

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This study investigated the risk of non-melanoma skin cancer (NMSC) in pre-dialysis patients with chronic kidney disease (CKD) and explored associated risk factors. A population-based cohort of 1,515,858 Taiwanese CKD patients was included. The standardized incidence ratio (SIR) for incident NMSC was determined. Compared with the general population, a 1.14-fold risk of NMSC was found in the CKD cohort. NMSC risk was significant in patients with pre-dialysis stage 5 CKD and anaemia (1.48-fold), and in those with uraemic pruritus after long-term antihistamine treatment (1.38-fold). A higher SIR for NMSC was found in younger patients with CKD (age < 70 years, 1.34-fold; age 20–39 years, 1.63-fold), stage 5 CKD with anaemia (age < 70 years, 2.09-fold), and uraemic pruritus (age <70 years, 2.22-fold). Pre-dialysis patients with CKD are at higher risk of NMSC, especially those with advanced-stage CKD, and those with uraemic pruritus.

Key words: non-melanoma skin cancer; chronic kidney disease; uraemic pruritus; epidemiology.

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Chronic kidney disease (CKD) is classified into 5 stages, mainly in accordance with measured or estimated glomerular filtration rate (GFR). Stage 5 CKD is defined as GFR <15 ml/min/1.73 m^2. Owing to decreased erythropoietin synthesis, patients with stage 5 CKD are usually anaemic, and typically eventually require renal replacement therapy (1). Pre-dialysis patients with CKD have demonstrated a higher incidence of kidney and urinary tract cancer than the general population (2–4), with the hazard ratios (HR) being maximum at the stage of needing chronic dialysis (5, 6). Jensen et al. (7) reported that the standardized incidence ratio (SIR) for squamous cell carcinoma was 4.8 among Denmark CKD patients, but was not elevated for basal cell carcinoma and melanoma; however, the study participants were confined to those aged <70 years who were hospitalized for CKD. The risk of skin cancer in the total cohort of CKD patients remains unclear.

Our previous study showed that chronic haemodialysis (HD) patients are at 1.58-fold higher risk of developing non-melanoma skin cancer (NMSC) compared with the general population (8), and that this risk is presumably related to chronic inflammation of uraemia. Uraemic pruritus (UP) is a manifestation of chronic systemic inflammation (9, 10) and its prevalence is approximately 42% in HD patients (11). The prevalence rate of UP in pre-dialysis CKD patients is positively associated with the progression of CKD (18% and 42% in stages 3 and 5 CKD, respectively) (12). HD patients with UP are at a 1.53-fold higher risk of NMSC compared with those without UP (8). In pre-dialysis CKD patients, the association between UP and NMSC has not been investigated.

Taiwan has the highest incidence and prevalence of CKD in the world (13). In 1995, the government of Taiwan established the National Health Insurance (NHI) programme, which includes 99% of Taiwanese residents. Using the National Health Insurance Research Database (NHIRD), we conducted a population-based study to investigate the risk and possible risk factors of NMSC in pre-dialysis patients with CKD.

MATERIALS AND METHODS

Data source and study participants

In this study, we obtained data recorded between 1999 and 2013 from the NHIRD, which contains healthcare data for 99% of the entire population of Taiwan (23.74 million people). All data are delinked information. We used the International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM) for diagnostic codes. This study was conducted with prior approval from the Ethics Committee and Human Subjects Institutional Review Board of Cardinal Tien Hospital.

We identified a CKD cohort comprised of patients newly diagnosed with CKD (who presented with at least one inpatient discharge diagnosis or 3 outpatient diagnoses codes of the following: ICD-9-CM 250.4, 274.1, 283.11, 403, 404, 440.1, 442.1, 447.3, 572.4, and 580–588 (which includes diabetes nephropathy, gouty nephropathy, hypertensive nephropathy, atherosclerosis/aneurysm/hyperplasia of renal artery, haemolytic uraemic syndrome, hepatorenal syndrome, nephrotic syndrome, glomerulonephritis and other nephritis, renal failure and renal sclerosis) (14) and had not commenced yet dialysis or renal transplantation), from 1 January 2000 to 31 December 2007 (enrolment period). Patients who had missing data, those aged <20 years, those who had NMSC within 12 months before CKD diagnosis, and those who were followed up for less than 3 months were excluded from this study. The CKD index date was defined as the first date of CKD diagnosis.

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Members of the reference group (general population cohort) for this study were identified from the longitudinal health insurance database 2005 (LHID 2005), a subset of the NHIRD. The LHID 2005 contains claims data from 1,000,000 individuals randomly sampled from the NHIRD in 2005. No statistically significant differences in age or sex distributions were found between the LHID 2005 and NHIRD. The general population cohort was screened using the same exclusion criteria as the CKD cohort. Because the various index dates of the CKD cohort were between 1 January 2000 and 31 December 2007, we selected a midpoint (1 January 2003) as the index date of the general population cohort.

Outcome measurements and subgroup analysis

The main outcome of interest in this study was the number of new cases of NMSC. The follow-up time for NMSC, defined as person-years at risk, began on the index date of each cohort. In the CKD cohort, the follow-up time ended on the date of NMSC diagnosis, death, at the start of dialysis or kidney transplant, or at the end of the study period (31 December 2013), whichever came first. In the general population, the follow-up time ended on the date of NMSC diagnosis or death, or was censored on 31 August 2011 to make the mean follow-up periods consistent between the CKD cohort and the general population. The occurrence of NMSC (ICD-9-CM 173) was defined as: (*i*) when a cancer catastrophic illness certificate was issued, or (*ii*) with the presence of at least one inpatient discharge diagnosis or 2 outpatient diagnoses and a procedure code for lesion removal. In the NHI system, the government defined several major diseases, such as cancer, as "catastrophic illnesses." A cytological or pathological report or evidence supporting the diagnosis of the malignancy was required for a patient to apply for a catastrophic illness certificate for cancer. We also used disease diagnosis codes and procedure codes (8, 15) to define NMSC, because many NMSC patients did not apply for a cancer catastrophic illness certificate for further adjuvant therapy after surgery.

The CKD cohort was subdivided into 2 groups, a stage 5 CKD with anaemia subcohort and a UP subcohort, for further analysis to clarify whether the stage of CKD or the presence of UP impacts the development of NMSC. Patients could belong to more than one subcohort.

The stage 5 CKD with anaemia subcohort was defined as patients with CKD who were given an erythropoietin-stimulating agent treatment (16) on or after the CKD index date, but prior to the end of follow-up. Based on NHI reimbursement regulations, patients with CKD in Taiwan who have a serum creatinine level of greater than 6 mg/dl (approximately equivalent to GFR <15 ml/min/1.73 m^2) and a haematocrit level of less than 28% can be treated with an erythropoiesis-stimulating agent. We defined the index date of stage 5 CKD with anaemia subcohort as the date of the first erythropoietin-stimulating agent prescription.

The UP subcohort was defined as patients with CKD who were administered with more than 6 weeks (17) or 42 defined daily dose (DDD) prescriptions of antihistamine and excluding those with diseases that might also need long-term antihistamine treatment (allergic rhinitis, chronic urticaria, psoriasis, and cutaneous T-cell lymphoma) (8) on or after the CKD index date and prior to the end of follow-up. In Taiwan, most patients with CKD with UP are treated by nephrologists, and are coded as having chronic renal failure, but without a specific code for UP, with antihistamines prescribed as the first-line UP treatment (18, 19). Hence, we defined the index date of UP subcohort as the first date of continuous antihistamine prescription. In subgroup analysis, the follow-up for NMSC started on the index date of each subcohort, and ended on a date identified with the same criteria similar to that of the CKD cohort.

Statistical analysis

All statistical analyses were performed using SAS statistical software (SAS System for Windows, version 9.3; SAS Institute, Cary, NC, USA). We calculated the expected number of NMSC in the CKD cohort and its subcohorts by multiplying the number of person-years accumulated in each stratum of sex; age (in 10-year strata); geographical regions (residents in northern or southern Taiwan divided by the Tropic of Cancer); and those receiving immunosuppressive therapy (immunosuppressant users were defined as ≥30 days-of-use, non-users were defined as no or <30 days-of-use), or not, by the corresponding specific rate of the general population cohort. The Tropic of Cancer runs through the centre of Taiwan; therefore, the northern and southern areas of Taiwan receive different amounts of ultraviolet radiation. The ethnicity of residents in northern and southern Taiwan, however, is identical (Asian ethnicity with skin phototypes III–V). The SIR, taken as the ratio of observed to expected number of cancer cases, was used as a measure of relative risk, and 95% confidence intervals (95% CIs) were calculated after assuming a Poisson distribution of the observed number of cancers.

RESULTS

A total of 702,633 participants met the inclusion criteria for the general population cohort. The mean age was 42.9 years, with 808 participants developing NMSC after a mean follow-up of 8.6 years. A total of 1,515,858 participants met the inclusion criteria for the CKD cohort. The mean age was 56.3 years, with 4,654 participants developing NMSC after a mean follow-up of 8.6 years. There was a higher proportion of southern Taiwan residents and immunosuppressant users in the CKD cohort than in the general population (**Table I**).

Table I. Demographic characteristics of the general population cohort, chronic kidney disease (CKD) cohort and subcohorts

	General population *n* = 702,633	CKD cohort *n* = 1,515,858	Subcohorts from CKD cohort	
			CKD-5[a] *n* = 66,918	UP[b] *n* = 25,294
Male, *n* (%)	344,407 (49.0)	788,091 (52.0)	32,099 (48.0)	13,223 (52.3)
Age at enrolment, mean±SD	42.9±15.8	56.3±17.3	63.3±13.3	66.4±14.9
20–39 years, *n* (%)	341,574 (48.6)	303,662 (20.0)	3,493 (5.2)	1,590 (6.3)
40–49 years, *n* (%)	153,924 (21.9)	262,866 (17.3)	7,818 (11.7)	2,377 (9.4)
50–59 years, *n* (%)	92,939 (13.2)	271,509 (17.9)	14,402 (21.5)	3,863 (15.3)
60–69 years, *n* (%)	61,540 (8.8)	281,553 (18.6)	17,973 (26.9)	5,362 (21.2)
≥70 years, *n* (%)	52,656 (7.5)	396,268 (26.1)	23,232 (34.7)	12,102 (47.8)
Geographical region, *n* (%)				
North	469,100 (66.8)	917,912 (60.6)	41,813 (62.5)	15,499 (61.3)
South	233,533 (33.2)	597,946 (39.4)	25,105 (37.5)	9,795 (38.7)
Immunosupp. users[c], *n* (%)	14,074 (2.0)	103,995 (6.9)	7,451 (11.1)	4,753 (18.8)
Follow-up, years, mean±SD	8.6±1.0	8.6±3.9	0.8±1.2	4.9±3.6
Total follow-up, person-years	6,009,818	13,021,937	55,588	123,214
New patients with NMSC, *n*	808	4,654	35	76
Annual incidence, per 100,000 person-years	13.4	35.7	63.0	61.7

[a]Defined as patients with CKD administered with erythropoietin-stimulating agent treatment during the follow-up period of CKD cohort. [b]Defined as patients with CKD administered with more than 6 weeks or 42 DDD prescriptions of antihistamine and excluding those with diseases that might also need long-term antihistamine treatment during the follow-up period of CKD cohort. [c]Defined as patients administered with more than 30 days prescriptions of immunosuppressant (immunosupp.). CKD-5: stage 5 CKD with anaemia; NMSC: non-melanoma skin cancer; SD: standard deviation; UP: uraemic pruritus.

In both the general population and CKD cohorts, the incidence of NMSC was higher in older patients; men (in both cohorts, men vs. women, men had a 1.2-fold higher risk, although there was no difference in risk after 70 years of age); those with residency in southern Taiwan (regarding north vs. south, there was an approximately lifelong 2-fold higher risk in southern residents in both cohorts); and those who were immunosuppressant users (in both cohorts, regarding users vs. non-users, users showed approximately 2-fold higher risk in age <50 years, but no difference in risk after 70 years of age) (**Fig. 1**). After adjustment for sex, age, geographical regions, and immunosuppressive therapy, the incidence rate of NMSC in the CKD cohort was elevated, compared with that of the general population (SIR 1.14; 95% CI, 1.11–1.18). The difference in risk between the CKD cohort and general population was higher in those of a younger age (SIR for ages 20–39 years, 1.63; 95% CI, 1.32–1.99) (**Table II**).

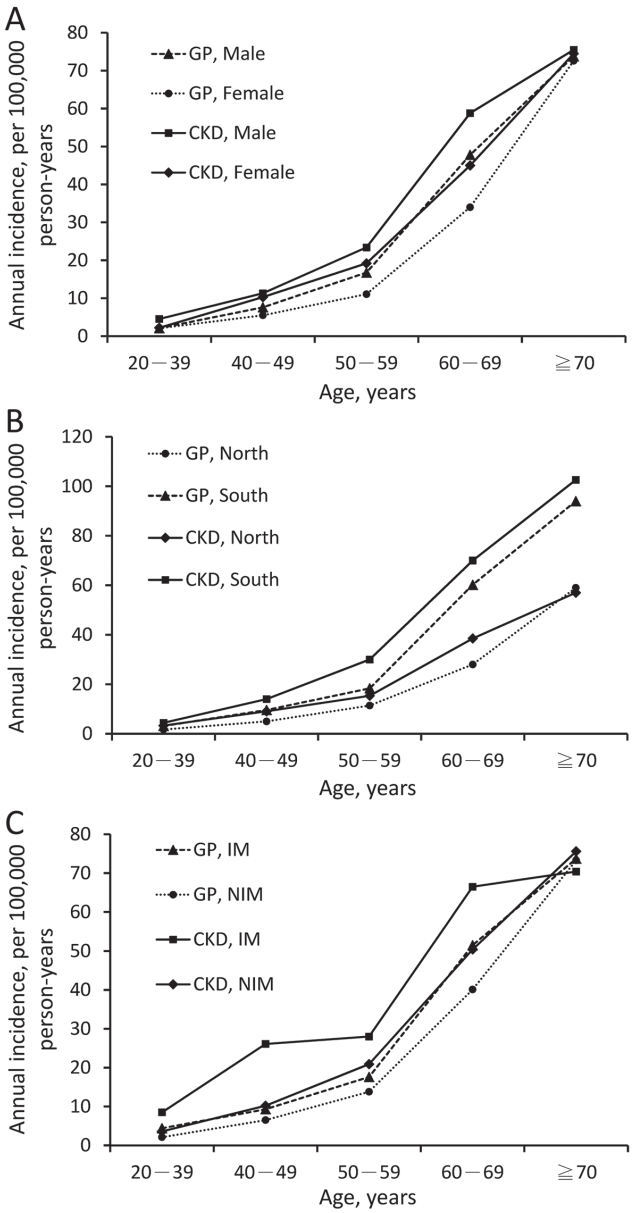

Fig. 1. Annual incidences for non-melanoma skin cancer (NMSC) in general population (GP) and pre-dialysis chronic kidney disease (CKD) patients. (A) Age- and sex-specific incidence. (B) Age and geographical region-specific annual incidence for NMSC in GP and pre-dialysis CKD patients. (C) Age and immunosuppression-specific annual incidence for NMSC in GP and pre-dialysis CKD patients. IM: immunosuppressant users; NIM: non-immunosuppressant users.

In the subcohort analysis, we observed an even higher incidence rate of NMSC in the subcohorts of stage 5 CKD with anaemia (SIR 1.48; 95% CI 1.03–2.06) and UP (SIR 1.38; 95% CI 1.08–1.72), compared with in the general population, following adjustment for sex, age, geographical regions, and immunosuppressive therapy. In the UP subcohort, only 202 patients (1% of UP patients) underwent ultraviolet-B (UVB) phototherapy. The SIR for NMSC was unchanged whether patients undergoing UVB phototherapy were included or excluded. We did not investigate the impact of UVB phototherapy on the development of NMSC because patients with CKD with UP undergoing UVB phototherapy were few in number. Younger patients had a higher SIR for NMSC (SIR for age <70 years 2.09; 95% CI 1.11–3.57 in the stage 5 CKD with anaemia subcohort; SIR for age <70 years 2.22; 95% CI 1.46–3.23 in the UP subcohort) than older patients, following adjustment for sex, age, geographical regions, and immunosuppressive therapy (**Fig. 2**).

DISCUSSION

This nationwide, population-based study confirmed that pre-dialysis patients with CKD carry a 1.14-fold higher risk of developing NMSC than those individuals in the general population after adjusting for sex, age, geographical regions, and immunosuppressive therapy. In addition, patients with stage 5 CKD with anaemia and those with UP carry a 1.48-fold and 1.38-fold higher risk of NMSC, respectively, compared with the general population. Among

Table II. Standardized incidence ratio (SIR) and 95% confidence interval (95% CI) of non-melanoma skin cancer in chronic kidney disease cohort

	n (%)	SIR (95% CI)
All patients, model 1	4,654 (100)	1.16 (1.12–1.19)
All patients, model 2	4,654 (100)	1.15 (1.11–1.18)
All patients, model 3	4,654 (100)	1.14 (1.11–1.18)
Sex		
Male	2,613 (56.1)	1.12 (1.08–1.16)
Female	2,041 (43.9)	1.17 (1.12–1.22)
Age at cohort entry		
20–39 years	97 (2.1)	1.63 (1.32–1.99)
40–49 years	247 (5.3)	1.60 (1.40–1.81)
50–59 years	496 (10.7)	1.49 (1.36–1.63)
60–69 years	1,257 (27.0)	1.23 (1.17–1.30)
≥ 70 years	2,557 (54.9)	1.02 (0.98–1.06)
Geographical regions		
North	2,112 (45.4)	1.11 (1.06–1.16)
South	2,542 (54.6)	1.17 (1.13–1.22)
Immunosuppressant		
Users[a]	472 (10.1)	1.12 (1.02–1.22)
Non-users[b]	4,182 (89.9)	1.15 (1.11–1.18)

[a]Defined as ≥ 30 days-of-use. [b]Defined as no or < 30 days-of-use. Models: 1: adjusted for sex and age. 2: adjusted for sex, age and geographical regions. 3: adjusted for sex, age, geographical regions and immunosuppressive therapy.

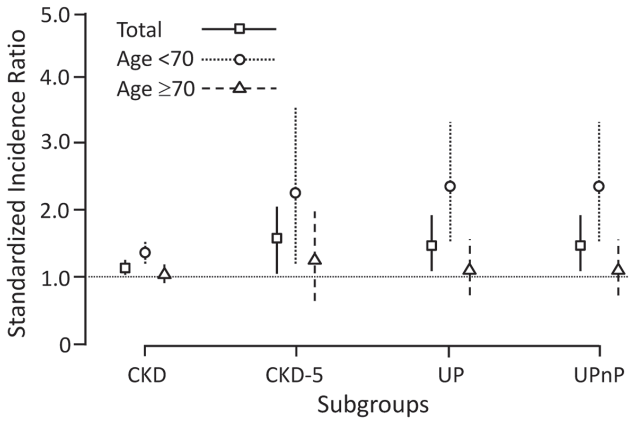

Fig. 2. Standardized incidence ratio and 95% confidence intervals for non-melanoma skin cancer in chronic kidney disease (CKD) cohort and the subcohorts. CKD-5: stage 5 CKD with anaemia; UP: uraemic pruritus; UPnP: uraemic pruritus with no ultraviolet B (UVB) phototherapy.

the total number of patients in the CKD cohort and subcohorts, the SIR for NMSC was higher in younger patients.

The pathogenesis for NMSC in patients with CKD might be related to the accumulation of uraemic toxins and reactive oxygen species, which further leads to chronic systemic inflammation, genomic damage, immune system dysfunction and DNA repair impairment (9, 20–22). The intensity of inflammation (23, 24) and genetic damage (25) increases when renal function decreases, and is at a maximum in HD patients. In this study, we found that patients with stage 5 CKD and anaemia carry a higher NMSC risk than those with early-stage CKD. The SIR for NMSC in patients with stage 5 CKD with anaemia is similar to those in patients on chronic HD (1.58-fold higher risk) (8).

Khanna et al. (12) found that the prevalence of UP is positively associated with CKD progression (18% and 42% in stages 3 and 5 CKD, respectively), whereas Solak et al. (26) reported that the prevalence of UP is not affected by CKD stage. Herein, pre-dialysis patients with CKD and UP carry a higher risk for NMSC than those without UP. These results are consistent with our previous study wherein chronic HD patients with UP were found to be at a higher risk of developing NMSC than those without UP (8).

Regional differences in UV radiation and factors of immunosuppression were adjusted for in this study. The latitude of Taiwan is 22–25°N, and the Tropic of Cancer runs through the centre of Taiwan. Residents in southern Taiwan (located in the tropical zone) carry a lifelong 2-fold higher risk for NMSC than those in northern Taiwan (located in the subtropical zone), both with respect to the general population and for patients with CKD. The difference in NMSC risk between the northern and southern general populations of Taiwan was consistent with the Taiwan cancer registry report (27). Immunosuppressive medications for the maintenance of transplant allografts or for the treatment of autoimmune diseases are associated with an increased risk for NMSC, especially squamous cell carcinoma (7, 28). There was a higher proportion of immunosuppressant users among the CKD cohort and the subcohorts than in the general population, probably because some CKD patients have an autoimmune cause for their renal diseases. Nevertheless, the SIR for NMSC in the CKD cohort and the subcohorts was significantly elevated after adjusting for the factors of geographical regions and immunosuppression.

Among the patients in the CKD cohort and the subcohorts, uraemia had a greater impact on the development of NMSC in younger patients, but this effect gradually diminished with increasing age. This was consistent with several previous reports showing that higher SIR was present in young HD patients for all cancers (5, 6, 8), and that higher HR was seen in young CKD men with regards to kidney cancer (2). In addition, immunosuppressive medications also had a higher impact on the development of NMSC in young participants of the general population and CKD cohort. This agreed with findings from a previous report that showed higher SIR for all cancers in young transplant recipients (5). A possible explanation for this is that uraemia and immunosuppression remove the protection against cancers from youth (5). Typically, the body's cancer defence system deteriorates and tumour suppressor genes are inactive in patients of advanced age (6). Therefore, the difference in NMSC risk between CKD patients and the general population, and between immunosuppressant users and non-users, could disappear with advancing age.

UVB exposure via sunlight is a risk factor for NMSC by induction of DNA photoproducts and UV-mediated immunosuppression (28). However, clinician-administered UVB phototherapy is provided at suberythemic doses, and a consistent association with NMSC risk has not been shown in this regard (29). We did not investigate the influence of UVB phototherapy on the development of NMSC in this study because very few pre-dialysis patients with CKD with UP were treated with UVB phototherapy. Because the SIR for NMSC was unchanged following the exclusion of patients treated with UVB phototherapy in the UP subcohort, we presumed that the increased incidence of NMSC related to UP is not caused by UVB phototherapy.

The strength of this study is that the Taiwan NHI programme covers 99% of Taiwanese residents, allowing for a true population-based design and avoiding selection bias. Study limitations include possible ascertainment bias, and a lack of obtainable relevant information in the NHIRD database. It is possible to misclassify NMSC based on the administrative database of NHIRD in Taiwan. Here, we further calculated the annual incidence of NMSC in the general population using cancer (27) and household registration (30) data of the corresponding age (≥20 years) and era (2003 to 2011); the result was 13.2 per 100,000 person-years, which was a consistent value with that from our study (13.4 per 100,000 person-years). The overall completeness of the Taiwan cancer registry from 2003 to 2011 is 94–98% (31). We defined UP as the prolonged prescription of antihistamines in pre-dialysis patients with CKD and excluded other diseases that might also

be treated with long-term antihistamines. This definition has been used in our previous study (8), although some level of misclassification might exist.

The NHIRD database did not document the laboratory data and the histological report of the patients. Therefore, we could not know the GFR (CKD stage) and NMSC types of patients. We used the prescription of erythropoiesis-stimulating agent to define stage 5 CKD with anaemia, but we could not define other stages of CKD. Based on the Taiwan cancer registry data, the definition of NMSC included basal cell carcinoma, squamous cell carcinoma, sarcomas (fibrosarcoma, angiosarcoma and others) and skin appendage cancers, in decreasing order of frequency in the general population (27). Carcinoma *in situ*, Kaposi's sarcoma and lymphoma were not included in our definition of NMSC. However, we could not know the type of NMSC in CKD patients. In addition, the risk of NMSC differs significantly among people with different skin colours. People of ethnicities other than Asian might require other studies to prove these associations.

In conclusion, this study provides novel findings that suggest that pre-dialysis patients with CKD are at a higher risk of developing NMSC than those individuals in the general population. Patients with advanced stages of CKD and the presence of UP with long-term antihistamine treatment carry an even greater risk for NMSC.

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