Dermatol Ther (Heidelb) (2023) 13:147–154
https://doi.org/10.1007/s13555-022-00858-z

REVIEW

# Characterizing Skin Cancer in Transplant Recipients by Fitzpatrick Skin Phototype

Chelsea N. Shope · Laura A. Andrews · Hannah Neimy · Courtney L. Linkous · Fatema Khamdan · Lara Wine Lee

Received: October 11, 2022 / Accepted: November 7, 2022 / Published online: December 5, 2022


## ABSTRACT

***Introduction***: Nearly half of organ transplants occur annually in patients with Fitzpatrick skin phototypes (Fitz type) III–VI. Organ transplant recipients (OTRs) are at risk for sequelae of chronic immunosuppression, of which skin cancer is common. As literature regarding skin cancer risk is largely conducted in OTRs with Fitz types I and II, we aimed to further characterize the incidence and risk factors for skin cancer in OTRs with higher Fitz types.

***Methods***: We conducted a retrospective review of OTRs with Fitz types III–VI evaluated by dermatology between 1 January 2012 and 1 June 2022. The primary outcome of this study was development of skin cancer post-transplant. Secondary outcomes included risk factors for skin cancer development. Data were analyzed using two-sample *t*-tests and Pearson's chi-squared.

***Results***: Of 530 OTRs, 193 had Fitz type III or higher. Ten patients (5.18%) developed 87 skin cancers and one recurrence at a mean of 5.17 years posttransplant. Patients with skin cancer self-identified as Black (70%, $p$-value $\leq 0.001$), male (70%, $p$-value $\leq 0.001$), and kidney transplant recipients (70%, $p$-value $\leq 0.001$), with a mean age of 58.20 years at transplant ($p$-value $\leq 0.001$). Subjects with skin cancer were more likely to be former smokers (60%) and prescribed tacrolimus ($p$-value $\leq 0.001$ each). Development of cutaneous squamous cell carcinoma (66, 75.86%) was most common, followed by basal cell carcinoma (17, 19.54%), and malignant melanoma (3, 3.45%). Skin cancer most often occurred on the face or scalp (60%, $p$-value = 0.027), though also developed in sun-protected sites (30%, $p$-value = 0.002). Verruca vulgaris was present in 10% of patients ($p$-value = 0.028).

***Conclusions***: Risk factors for skin cancer post-transplant differ in OTRs with higher Fitz types. Our results suggest that among OTRs who self-identified as Black, kidney recipients are at

C. N. Shope (✉) · L. A. Andrews · H. Neimy · C. L. Linkous
College of Medicine, Medical University of South Carolina, 135 Rutledge Avenue, 11th Floor, Charleston, SC 29425, USA
e-mail: shopec@musc.edu

F. Khamdan
Department of Pathology & Lab Medicine, Medical University of South Carolina, Charleston, SC, USA

F. Khamdan
Department of Dermatology, Salmaniya Medical Complex, Manama, Kingdom of Bahrain

L. W. Lee
Department of Dermatology & Dermatologic Surgery, Medical University of South Carolina, Charleston, SC, USA

L. W. Lee
Department of Pediatrics, Medical University of South Carolina, Charleston, SC, USA

increased risk for skin cancer in non-sun-exposed regions. These cancers may be associated with human papillomavirus (HPV). Education is key for preventing morbidity and mortality secondary to skin cancer.

**Keywords:** Immunosuppression; Transplant; Cutaneous malignancy; Squamous cell carcinoma; Basal cell carcinoma; Malignant melanoma

**Key Summary Points**

Solid organ transplant recipients with Fitzpatrick skin phototypes III–VI are at risk for skin cancer post-transplant; therefore, patients should be educated on self-skin exams and referred to dermatology for new or changing lesions.

Some risks for skin cancer are the same among organ transplant recipients regardless of race or ethnicity. However, thoracic transplant (heart or lung) increases risk for skin cancer in organ transplant recipients with Fitzpatrick skin phototypes I and II, while kidney transplant increases risk for skin cancer in organ transplant recipients with Fitzpatrick skin phototypes III–VI.

Like organ transplant recipients with Fitzpatrick skin phototypes I and II, recipients with higher Fitzpatrick skin phototypes are most frequently diagnosed with cutaneous squamous cell carcinoma of the head and neck. However, organ transplant recipients are also at risk for skin cancers in sun-protected sites such as the groin and genitals.

## INTRODUCTION

In 2021, more than 41,000 transplants were performed in the USA, representing an annual record for the ninth consecutive year [1]. As transplants continue to increase and patients survive longer, the sequelae of chronic immunosuppression will become more prevalent [2]. Organ transplant recipients (OTRs) are at increased risk for malignancies, the most common of these being skin cancer [3]. OTRs are at a 65–250-fold increased risk for cutaneous squamous cell carcinoma (cSCC) [2], a tenfold increased risk for basal cell carcinoma (BCC), and a threefold increased risk for malignant melanoma (MM), along with other rare cutaneous neoplasms [4]. However, literature supporting these data is largely from kidney transplant recipients with Fitzpatrick skin phototypes (Fitz type) I and II [5]. While patients with Fitz types III–VI are thought to have lower risks of developing skin cancer as compared with their lower Fitz types, they are at increased risk of skin cancer compared with their immunocompetent peers [6]. We sought to describe the incidence of skin cancer in OTRs with higher Fitz types at our institution and identify associated risk factors. Improving understanding of skin cancer incidence in this group may contribute to improved screening tools and post-transplant guidelines that assist in the recognition of relevant racial healthcare disparities.

## METHODS

We conducted a retrospective review of OTRs seen by dermatology at our institution between 1 January 2012 and 6 January 2022, which represents the time our institution's electronic health recorded was implemented to the time the study began. During the study period, our institution performed a mean of 375 transplants per year. Of these, 7.77% were seen by dermatology. Patients seen by dermatology either reported dermatologic complaints or had lesions of concern. We stratified OTRs on the basis of self-identified race or ethnicity. Patients who self-identified as white, representing Fitz types I and II, were excluded. Data pertaining to patient demographics, medical history, transplant course, and dermatologic history were collected. Patients were then stratified by occurrence of skin cancer post-transplant.

Data analysis was conducted using SPSS Statistics 28 (IBM, Armonk, NY) for the primary outcome of skin cancer development. Cohort demographics were evaluated using descriptive statistics. Data were analyzed using chi-squared or paired *t*-tests.

IRB approval was provided by the Medical University of South Carolina IRB I for Pro00117311, on 10 January 2022. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## RESULTS

Of the 530 OTRs identified, 193 had Fitz type of III or higher. Patients were most often male (52.85%) and self-identified as Black (91.70%), with a mean age at transplant of 47.04 years (±15.88 years). Only one patient had a pre-transplant history of skin cancer, and one patient had a family history of skin cancer (Table 1).

Ten patients (5.18%) developed 87 skin cancers and one recurrence post-transplant. Patients who developed skin cancer were more often male (70%, $p$-value $\leq 0.001$), kidney transplant recipients (70%, $p$-value $\leq 0.001$), who self-identified as Black (70%, $p$-value $\leq 0.001$), with a mean age of 58.20 years at transplant. This is compared with a mean age of 46.43 years at transplant in OTRs who did not develop skin cancer post-transplant ($p$-value $\leq 0.001$). Liver transplant recipients were less likely to develop posttransplant skin cancer (20%, $p$-value = 0.010) (Table 1).

Pretransplant history of skin cancer was a predictor for post-transplant skin cancer development (10%, $p$-value = 0.002). OTRs who developed skin cancer posttransplant were more frequently former smokers (60%, $p$-value $\leq 0.001$). They were also more likely to be prescribed cyclosporine (30%, $p$-value = 0.007). There was a trend toward significance for use of tacrolimus (70%, $p$-value = 0.070) and azathioprine (10%, $p$-value = 0.071). Common comorbidities, such as hypertension, type 2 diabetes mellitus, hyperlipidemia, and coronary artery disease were not associated with skin cancer development (Table 2).

Patients most often developed cSCC (66, 75.86%), followed by BCC (17, 19.54%), MM (3, 3.45%), and one spindle cell adenocarcinoma. Skin cancer development occurred at a mean of 5.17 years post-transplant. Type of first skin cancer was BCC (60%, $p$-value = 0.014) or cSCC (40%, $p$-value = 0.045) most often occurring on the face or scalp (60%, $p$-value = 0.027). Skin cancers developed in sun-protected sites in 30% of patients ($p$-value = 0.002), which includes the buttocks and inguinal folds. There was a tendency for skin cancer to recur in the same location (10%, $p$-value $\leq 0.001$). A diagnosis of verruca vulgaris (VV) was present in 10% of patients with skin cancer ($p$-value = 0.028) (Table 3).

## DISCUSSION

The risk of skin cancer is considerably elevated in OTRs, with reports indicating at least a 100-fold increased risk when compared with the general population, without consideration of Fitz type [7, 8]. Of the approximately 41,000 total OTRs in 2021, almost half were patients with Fitz types III–VI [1]. However, OTRs with higher Fitz types are underrepresented in studies of skin cancer post-organ transplant.

Risk factors for skin cancer development in OTRs include male gender, age ≥ 50 years, pre-transplant history of skin cancer, and Fitz type I or II [7]. Among OTRs with higher Fitz types in our cohort, male gender, older age at transplant, and pretransplant history of skin cancer remained risk factors for post-transplant skin cancer. However, patients who self-identified as Black, as compared with American Indian/Alaska Native and Hispanic or Latino patients, were more likely to develop skin cancer in our cohort. Smoking status was also a risk factor.

Type of organ transplant may confer variable levels of risk for developing skin cancer in OTRs [9], with the greatest reported risk associated with thoracic organ transplants [3]. In our cohort, however, risk was highest among kidney recipients. Similar to reported literature, we found risk for post-transplant skin cancer to be

**Table 1** Patient demographics for solid organ transplant recipients with Fitzpatrick skin phototypes III–VI, stratified by the presence or absence of skin cancer development posttransplant

| | All transplant recipients | Transplant recipients with posttransplant skin cancer | Transplant recipients without development of posttransplant skin cancer | *p*-Value |
|---|---|---|---|---|
| Age at time of transplant (years) | 47.04 | 58.20 | 46.43 | $\leq 0.001$* |
| Self-identified race (*n*, %) | | | | $\leq 0.001$* |
| African American | 177 (91.7%) | 7 (70.0%) | 170 (92.9%) | |
| American Indian/Alaska Native | 2 (1.0%) | 1 (10.0%) | 1 (0.5%) | |
| Asian | 7 (3.6%) | 0 (0.0%) | 7 (3.8%) | |
| Hispanic or Latino | 6 (3.1%) | 2 (20.0%) | 4 (2.2%) | |
| Pacific Islander | 1 (0.5%) | 0 (0.0%) | 1 (0.5%) | |
| Gender (*n*, %) | | | | $\leq 0.001$* |
| Female | 91 (47.1%) | 3 (30.0%) | 88 (48.1%) | |
| Male | 102 (52.9%) | 7 (70.0%) | 95 (51.9%) | |
| Type of organ transplanted (*n*, %)[a] | | | | $\leq 0.001$* |
| Kidney | 163 (84.5%) | 7 (70.0%) | 156 (85.2%) | |
| Liver | 8 (4.1%) | 2 (20.0%) | 6 (3.3%) | |
| Heart | 19 (9.8%) | 1 (10.0%) | 18 (9.8%) | |
| Lung | 2 (1.0%) | 0 (0.0%) | 2 (1.1%) | |
| Pancreas | 19 (9.8%) | 1 (10.0%) | 18 (9.8%) | |

*Indicates statistically significant result ($p$-value $\leq 0.05$)

[a]Patients may have received more than one organ type, i.e., kidney and pancreas transplant

lowest among liver recipients. Notably, kidney transplants comprised the overwhelming majority of our SOC cohort, which is representative of trends in organ transplantation nationwide [1].

Skin cancer risk is thought to stem from long-term administration of posttransplant immunosuppressive therapies that dampen immune system surveillance, impair the repair of UV-induced DNA damage, and increase the potential for reactivation of certain oncogenic

**Table 2** Risk factors for skin cancer development in organ transplant recipients with Fitzpatrick skin phototypes III–VI

| | Transplant recipients with posttransplant skin cancer | Transplant recipients without development of posttransplant skin cancer | *p* value |
|---|---|---|---|
| Smoking status (*n*, %)[a] | | | ≤ 0.001* |
| Never smoker | 4 (40.0%) | 113 (61.7%) | |
| Current smoker | 0 (0.0%) | 8 (4.4%) | |
| Former smoker | 6 (60.0%) | 62 (33.8%) | |
| Personal history of pretransplant skin cancer (*n*, %) | | | 0.002* |
| Yes | 1 (10.0%) | 0 (0.0%) | |
| No | 9 (90.0%) | 183 (100.0%) | |
| Family history of skin cancer (*n*, %) | | | 0.815 |
| Yes | 0 (0.0%) | 1 (0.5%) | |
| No | 10 (100.0%) | 182 (99.5%) | |
| Transplant medications[b] | | | |
| Tacrolimus | 7 (70.0%) | 163 (89.1%) | 0.070 |
| Azathioprine | 1 (10.0%) | 3 (1.6%) | 0.071 |
| Cyclosporine | 3 (30.0%) | 12 (6.6%) | 0.007* |
| Comorbid conditions | | | |
| Hypertension | 8 (80.0%) | 150 (82.0%) | 0.875 |
| Type 2 diabetes | 3 (30.0%) | 85 (46.4%) | 0.309 |
| Hyperlipidemia | 6 (60.0%) | 67 (36.6%) | 0.138 |
| Coronary artery disease | 0 (0.0%) | 49 (26.8%) | 0.058 |
| Chronic kidney disease | 7 (70.0%) | 109 (59.6%) | 0.512 |
| Other malignancy | 1 (10.0%) | 16 (8.7%) | 0.891 |

*Indicates statistically significant result (*p*-value ≤ 0.05)
[a]Indicates smoking status at time chart review was performed
[b]Refers to use of these medications at any point from time of transplant to time chart review was performed. Patients may have been prescribed more than one of these medications

viruses [10]. Specific immunosuppressive drugs may positively or negatively influence the risk of skin cancer development [7]. Similar trends were noted in our cohort. Sun avoidance is recommended for patients taking azathioprine owing to drug-metabolite-induced UVA photosensitivity and impaired nucleotide excision repair [7, 11]. Usage of calcineurin inhibitors (CNIs), such as tacrolimus and cyclosporin, may result in upregulation of the potentially oncogenic activating transcription factor 3

**Table 3** First skin cancers posttransplant among transplant recipients with Fitzpatrick skin phototypes III–VI

| Type of skin cancer | *n* (%) |
|---|---|
| Squamous cell carcinoma | 4 (40.0%) |
| SCCis* | 3 (30.0%) |
| Invasive+ | 1 (10.0%) |
| Basal cell carcinoma | 6 (60.0%) |
| Melanoma in situ | 0 (0.0%) |
| Location of skin cancer | Count (%) |
| Scalp | 3 (30.0%) |
| Face | 3 (30.0%) |
| Chest or back | 1 (10.0%) |
| Lower extremities | 1 (10.0%) |
| Other[a] | 2 (20.0%) |
| Additional skin cancers | Count (%) |
| Yes | 5 (50.0%) |
| No | 5 (50.0%) |
| Recurrence | 1 (10.0%) |

*SCCis: Squamous cell carcinoma in situ
[a]Groin and buttocks

(ATF3), increased UVA photosensitivity, and altered nucleotide excision repair [7, 12].

It has been reported that in OTRs who self-identify as Black with Fitz types V or VI, skin cancer diagnoses are not uncommonly located in sun-protected sites [13]. In our cohort, nearly one-third of skin cancer occurred in sun-protected sites, including the groin and buttocks. As skin cancer is less prevalent in Fitz types V or VI, and not uncommonly occurs in sun-protected areas, Black OTRs are more likely to have skin cancer diagnosed at advanced stages, thus increasing their risk of morbidity and mortality [6]. Additionally, HPV DNA is three times more likely to be present in cSCCs arising in immunocompromised versus immunocompetent patients. The mechanism is complex and proposed to be owing to a complex interplay between HPV infection and impaired DNA repair or apoptosis of UV-damaged cells, or simply may underscore the susceptibility of immunocompromised patients to develop HPV infection and cutaneous malignancy [14, 15]. Nonetheless, in Black OTRs, skin cancer diagnoses are frequently HPV positive, and/or associated with a history of condyloma acuminata or VV [6, 16]. Within our cohort, VV was present in a number of patients who developed posttransplant skin cancer, suggesting that screening for and treating HPV infection pretransplant may be an important preventative measure.

Limitations of our study include the retrospective nature, monocentric design, and small sample size for patients developing skin cancer posttransplant. Owing to the retrospective nature of this study, history of sunburn and sun exposure were not available/collected, however, as this may contribute to the formation of secondary cancers, future studies correlating sunburn/sun exposure history and skin cancer posttransplant are warranted. No patients self-identifying as Asian or Pacific Islander who developed posttransplant skin cancer are included in our cohort. Additionally, we were unable to include OTRs evaluated by dermatology outside of our institution, or those without dermatologic symptoms or lesions that prompted referral to dermatology.

## CONCLUSIONS

While skin cancer development post-transplant may be lower in OTRs with higher Fitz types, risk for skin cancer nonetheless exists. Similar to prior studies, our study demonstrates that skin cancer diagnosis in OTRs with higher Fitz types differs from diagnosis in their counterparts with Fitz types I or II. Skin cancer observed in OTRs with higher Fitz types may be more aggressive owing to later stage at diagnosis, which portends a greater risk for recurrence and metastasis [7]. OTRs who self-identify as Black may be at particularly high risk as compared with other patients with higher Fitz types. The results of our study can inform improvements in skin cancer education and screening in OTRs with

Fitz types III–VI, as well as highlight the need for provider education.

## ACKNOWLEDGEMENTS

The authors would like to thank Dr. Mat Gregoski, PhD, for his statistical analysis. We would also like to thank the South Carolina Translational Research (SCTR) institute for identifying study subjects, and the participants of the study for making this project possible.

***Funding.*** No funding or sponsorship was received for this study or publication of this article.

***Authorship Contributions.*** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Chelsea Shope, Laura Andrews, Hannah Neimy, Courtney Linkous, and Fatema Khamdan. The first draft of the manuscript was written by Chelsea Shope and Hannah Neimy, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

***Prior Presentation.*** Preliminary results from this study were presented as poster at the Skin Cancer Symposium + Symposium for Inflammatory Skin Disease on June 11, 2022, which took place virtually.

***Disclosures.*** Chelsea Shope, Laura Andrews, Hannah Neimy, Courtney Linkous, Fatema Khamdan, and Lara Wine Lee declare that they have no conflict of interests to disclose.

***IRB Approval.*** IRB approval was obtained for this study at the Medical University of South Carolina, Pro00117311, on January 10, 2022.

***Compliance with Ethics Guidelines.*** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

***Data Availability.*** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.



## REFERENCES

1. National Data. https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/. Published 2022. Accessed June 1, 2022.

2. Greenberg JN, Zwald FO. Management of skin cancer in solid-organ transplant recipients: a multidisciplinary approach. Dermatol Clin. 2011;29(2):231–41.

3. Jambusaria-Pahlajani A, Crow LD, Lowenstein S, et al. Predicting skin cancer in organ transplant recipients: development of the SUNTRAC screening tool using data from a multicenter cohort study. Transpl Int. 2019;32(12):1259–67.

4. Zwald F, Leitenberger J, Zeitouni N, et al. Recommendations for solid organ transplantation for transplant candidates with a pretransplant diagnosis of cutaneous squamous cell carcinoma, Merkel cell carcinoma and melanoma: a consensus opinion from the international transplant skin cancer collaborative (ITSCC). Am J Transplant. 2016;16(2):407–13.

5. Acuna SA, Huang JW, Scott AL, et al. Cancer screening recommendations for solid organ transplant recipients: a systematic review of clinical practice guidelines. Am J Transplant. 2017;17(1): 103–14.

6. Pritchett EN, Doyle A, Shaver CM, et al. Non-melanoma skin cancer in nonwhite organ transplant recipients. JAMA Dermatol. 2016;152(12): 1348–53.

7. Stevenson ML, Carucci J, Colegio OR. Skin cancer in transplant recipients: Scientific retreat of the international immunosuppression and transplant skin cancer collaborative and skin care in organ transplant patients-Europe. Clin Transplant. 2019;33(12): e13736.

8. Garrett GL, Lowenstein SE, Singer JP, He SY, Arron ST. Trends of skin cancer mortality after transplantation in the United States: 1987 to 2013. J Am Acad Dermatol. 2016;75(1):106–12.

9. Elnahas S, Olson MT, Kang P, et al. Factors associated with skin cancer in lung transplant recipients: a single-center experience. Clin Transplant. 2019;33(12): e13718.

10. Plasmeijer EI, Jiyad Z, Way M, et al. Extreme incidence of skin cancer in kidney and liver transplant recipients living with high sun exposure. Acta Derm Venereol. 2019;99(10):929–30.

11. Perrett CM, Walker SL, O'Donovan P, et al. Azathioprine treatment photosensitizes human skin to ultraviolet A radiation. Br J Dermatol. 2008;159(1): 198–204.

12. Jung JW, Overgaard NH, Burke MT, et al. Does the nature of residual immune function explain the differential risk of non-melanoma skin cancer development in immunosuppressed organ transplant recipients? Int J Cancer. 2016;138(2):281–92.

13. Chung CL, Nadhan KS, Shaver CM, et al. Comparison of posttransplant dermatologic diseases by race. JAMA Dermatol. 2017;153(6):552–8.

14. Iannacone MR, Wang W, Stockwell HG, et al. Sunlight exposure and cutaneous human papillomavirus seroreactivity in basal cell and squamous cell carcinomas of the skin. J Infect Dis. 2012;206(3):399–406.

15. Nagarajan P, Asgari MM, Green AC, et al. Keratinocyte carcinomas: current concepts and future research priorities. Clin Cancer Res. 2019;25(8): 2379–91.

16. Borik L, Balagula Y, Hinds GA, Loss MJ. Non-melanoma skin cancers in African American solid organ transplant recipients: regional bias or a real need for surveillance? Eur J Dermatol. 2017;27(5): 530–1.