Clinical Drug Investigation (2019) 39:197–203
https://doi.org/10.1007/s40261-018-0732-3

ORIGINAL RESEARCH ARTICLE

Comparison of Skin Cancer Incidence in Caucasian and Non-Caucasian Liver Vs. Lung Transplant Recipients: A Tale of Two Regimens

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Published online: 23 November 2018

Abstract

Background Organ transplantation is a significant risk factor for the development of skin cancer. The impact of skin type, immunosuppressive regimens, and photosensitizing agents requires further study.

Objective The objective of this study was to compare skin cancer development between Caucasian and non-Caucasian transplant recipients at the University of Southern California.

Methods We performed a retrospective chart review of lung and liver transplantations to determine the incidence of post-transplant skin cancer. Participants included patients who underwent lung or liver transplantation between 2005 and 2013 at our institution. Patients included in the study were limited to those who survived through the study observation period.

Results We analyzed 475 patients who underwent transplantation, including 370 liver transplant recipients and 105 lung transplant recipients. Among these, 46.3% identified as Caucasian, while 53.7% were non-Caucasian. Over a mean follow-up of 7.9 years, 11.8% of Caucasian patients developed at least one skin cancer, compared with 2.7% of non-Caucasians ($p < 0.001$). However, irrespective of race, skin cancer development was significantly greater in lung compared with liver transplant recipients (20.0% vs. 3.2%, $p < 0.001$). The standard immunosuppressive and prophylactic regimens were mycophenolate mofetil and tacrolimus based for both transplants. Mycophenolate mofetil was maintained throughout the course in lung transplant patients, whereas this agent was reduced and terminated when possible in liver transplant recipients. In addition, during the years examined, voriconazole, a known photosensitizing agent, was used in lung transplant recipients to prevent aspergillosis.

Conclusions Fair skin type increases post-transplant skin cancer development, irrespective of the immunosuppressive regimen. A higher risk of skin cancer is associated with different regimens; in particular photosensitizing agents may increase risk in transplant recipients.

Key Points

Skin cancer development after liver and lung transplantation is greater in Caucasians than non-Caucasians.

Lung transplantation is associated with higher risk compared with liver transplantation, possibly owing to increased concentrations of immunosuppressive agents and the adjunctive use of voriconazole, a photosensitizing agent.

Fairer skin type and photosensitizing drugs appear to increase the risk of post-transplant skin cancer.

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1 Introduction

Organ transplantation is associated with a significantly elevated risk of skin cancer development, which is largely related to the need for prolonged immunosuppression to prevent graft rejection [1–3]. It is estimated that up to 50% of Caucasian individuals in Western countries will develop at least one non-melanoma skin cancer, more recently termed keratinocyte skin cancer, in the first two decades after transplantation [1, 3]. Moreover, these cancers tend to be more aggressive with higher associated morbidity and mortality than those that arise in the general population [4]. Transplant patients are most susceptible to the development of squamous cell carcinoma (SCC), with estimates of 30–100 times higher rates, as compared with general population rates [4, 5]. Increased rates of basal cell carcinoma (BCC) and melanoma are observed as well, although these increases are less striking [1].

The recognized risk factors for the development of skin cancer include advanced age, immunosuppression, fair skin tones (Fitzpatrick Skin Types I–III), and cumulative ultraviolet (UV) radiation exposure [6, 7]. Previously published studies on skin cancer risk factors in post-transplant patients have low numbers of non-Caucasian patients in study cohorts [2]. In some cases, patients with darker skin types are excluded from studies because of the low incidence of skin cancer among these patients. Given that 40% of transplant recipients in USA are individuals of skin of color (Fitzpatrick Skin Types IV–IV), a greater understanding of risk profiles by race and skin type is vital to guide surveillance, patient counseling, and to reduce morbidity and mortality associated with skin cancer in transplant patients [2].

In this study, we compared rates of skin cancer between lung and liver transplant recipients at the Keck University of Southern California Medical Center, contrasting Caucasian and non-Caucasian individuals. We specifically chose to investigate these two transplant programs because of the homogeneous antirejection regimens employed for these two organs at the Keck University of South California over a prolonged period of time. Our aim was to better characterize the impact of skin of color on the risk of skin cancer development after organ transplantation.

2 Patients and Methods

This study was conducted as an institutional board review-approved retrospective review of patients who underwent lung or liver transplantation at Keck Medical Center at the University of Southern California between 2005 and 2013. Patient records for liver transplants were obtained through Keck Hospital's UNOS/UNET transplant patient database and were matched against the OTTR database to create a reliable and comprehensive list of medical record numbers by which patient records could be searched. Records from the Keck Lung Transplant Program were obtained directly.

We compiled occurrences of SCC (including SCC in situ/Bowen's disease), BCC, and melanoma, along with data on age, sex, race, and previous personal and family history of any cancer type. Data on histologically confirmed skin cancer were obtained from a review of the electronic medical record. Pathology reports were referenced when available. Information regarding patient race was gathered from the demographic section of the electronic medical record. Patient race was categorized Caucasian or non-Caucasian, with the latter including Hispanic, African-American, Asian, Pacific Islander, and Native American populations. Relative skin cancer rates between Caucasian and non-Caucasian patient groups were then calculated. For the analysis of post-transplant skin cancer in general, patients were included in the skin cancer group if they developed at least one post-transplant skin cancer; however, for analyses of skin cancer subtypes (SCC or BCC), each individual malignancy was included.

The average follow-up duration was calculated from the time beginning from the date of transplant for each patient to the date of initiation of our study. The incidence rate of skin cancer was calculated from the number of skin cancers developed per year of follow-up for each patient.

The 1- and 3-year survival rates for liver transplant recipients at our institution during the study period were 87.9% and 84.1%, respectively. For lung transplant recipients at our institution, the 1- and 3-year survival rates were 75.5% and 60.0%, respectively. Given the high mortality observed among lung transplant recipients, to achieve comparability, we excluded those who did not survive through the entire observation period. In addition, a complete record of post-transplant ongoing follow-up was required for inclusion in the study.

We used SPSS statistical analysis software, Version 22.0 (SPSS Inc., Chicago, IL, USA) to analyze the study data. The Student's t test and the Chi square test were employed to analyze continuous variables and categorical variables, respectively. Comparisons of ratios were performed with Kruskal–Wallis non-parametric methods. All statistical tests were two-tailed with the significance level set at $p < 0.05$.

3 Results

Initially, 658 transplant patients who were living at the onset of the study were identified (548 liver transplant recipients and 110 lung transplant recipients). Of these, 117 patients

(112 liver transplant recipients and five lung transplant recipients) were excluded because no post-transplant follow-up record was available. Our final dataset consisted of 475 patients who had undergone either lung or liver organ transplantation at our institution. The mean post-transplantation follow-up duration was 7.9 years (standard deviation 3.4). In our cohort, 370 (77.9%) were status post-liver transplantation and 105 (22.1%) were status post-lung transplantation. In our dataset, 46.3% were identified as Caucasian, while 53.7% were non-Caucasian (Table 1). There were no significant differences between Caucasian and non-Caucasian patients with regard to age, sex, history of pre-transplant cancer of any type, or family history of cancer of any type (Table 1). Compared with lung transplant patients, those who underwent liver transplantation were more likely to be male, older, non-Caucasian, and to have a previous history of cancer of any type (Table 1).

Among liver and lung transplant recipients included in the study, 11.8% of Caucasian patients developed at least one skin cancer, compared with 2.7% of non-Caucasian patients ($p < 0.001$). Specifically, the rate of SCC development was 10.0% vs. 2.4% in Caucasians and non-Caucasians, respectively, ($p < 0.001$). Compared with the non-Caucasian cohort, the Caucasian data suggested a trend towards a higher rate of BCC (3.2% vs. 0.4%, $p = 0.08$) and melanoma (0.8% vs. 0%, $p = 0.99$); however, these differences did not reach statistical significance (Table 2). Overall, the relative risk of developing a skin cancer in Caucasian compared with non-Caucasian patients was 4.31 (95% confidence interval 1.9–9.7) (Table 2).

Skin cancer was identified in 20% of lung transplant recipients over 9.1 years (standard deviation 5.6), compared with 3.2% in liver transplant recipients over a mean post-transplant follow-up of 6.4 years (standard deviation 2.9 years) ($p < 0.001$). To circumvent the difference in post-transplant follow-up duration, we calculated the mean annual incidence rate of skin cancer showing that it was significantly higher in lung transplant recipients (0.02 vs. 0.006 per patient/year, $p < 0.001$) (Table 3).

Given that the proportion of Caucasian patients within our lung transplant population was significantly higher than in the liver transplant group, we then performed sub-analyses restricted to either Caucasian or non-Caucasian patients. In a sub-analysis restricted to Caucasian patients only, there was a significantly elevated rate of skin cancer in Caucasian lung vs. liver transplant patients (25.8% vs. 2.4%, $p < 0.001$), with a calculated relative risk of 6.7 (95% confidence interval 3.06–14.5) (Table 2). Correcting for duration of exposure post-transplant, the annual incidence rate of skin cancer development was higher in

Table 1 Features of Caucasian vs. non-Caucasian patients and lung vs. liver transplant recipients

Characteristics	Caucasian ($n = 220$)	Non-Caucasian ($n = 255$)	*P* value
Male, *n* (%)	124 (56.4)	150 (58.8)	0.62
Age, y, mean (SD)	57.3 (12.9)	59.1 (11.3)	0.09
Race breakdown, *n* (%)	n/a	Hispanic 198 (77.6) Black 14 (5.5) Asian 40 (15.7) Pacific Islander 2 (0.78) Native American 1 (0.40)	n/a
Previous Hx of cancer (any type)[a], *n* (%)	46 (20.9)	67 (26.3)	0.20
Family Hx of cancer (any type)[a], *n* (%)	26 (11.8)	24 (10.7)	0.45
	Lung ($n = 105$)	Liver ($n = 370$)	
Male, *n* (%)	51 (48.6)	223 (60.3)	0.03
Age, y, mean (SD)	52.7 (15.9)	59.8 (10.2)	<0.001
Non-Caucasian, *n* (%)	39 (37.1)	216 (58.4)	<0.001
Race breakdown, *n* (%)	Caucasian: 66 (62.9) Hispanic 32 (30.5) Black 5 (4.76) Asian 2 (1.9) Pacific Islander 0 (0) Native American 0 (0)	Caucasian: 154 (41.6) Hispanic 166 (44.9) Black 9 (2.4) Asian 38 (10.2) Pacific Islander 2 (0.54) Native American 1 (0.27)	n/a
Previous Hx of cancer (any type), *n* (%)	15 (14.3)	98 (26.5)	0.009
Family Hx of cancer (any time), *n* (%)	9 (8.6)	41 (11.1)	0.58

Hx history, *n/a* not applicable, *SD* standard deviation

[a]Any type of cancer, including skin or other type

Table 2 Skin cancer incidence in Caucasian vs. non-Caucasian patients and lung vs. liver transplant recipients

Type of cancer	Caucasian ($n=220$)	Non-Caucasian ($n=255$)	Relative risk (95% CI)	P value
Skin cancer, n (%)	26 (11.8)	7 (2.7)	4.31 (1.91–9.73)	< 0.001
SCC, n (%)	22 (10.0)	6 (2.4)	4.25 (1.75–10.29)	< 0.001
BCC, n (%)	7 (3.2)	1 (0.4)	8.11 (0.97–65.44)	0.08
Melanoma, n (%)	1 (0.8)	0	n/a	0.99
	Lung ($n=105$)	Liver ($n=370$)	Relative risk (95% CI)	P value
Skin cancer, n (%)	21 (20.0)	12 (3.2)	6.17 (3.14–12.12)	< 0.001
SCC, n (%)	20 (19.0)	9 (2.4)	7.83 (3.68–16.68)	< 0.001
BCC, n (%)	5 (4.8)	4 (1.1)	4.40 (1.20–16.11)	0.03
Melanoma, n (%)	1 (1.0)	0 (0)	n/a	0.99
Skin cancer (Caucasian only), n (%)	17 (25.8)	9 (2.4)	6.65 (3.06–14.50)	< 0.001
Skin cancer (non-Caucasian only), n (%)	4 (10.3)	3 (0.8)	4.70 (1.07–20.66)	0.01

BCC basal cell carcinoma, *CI* confidence interval, *n/a* not applicable, *SCC* squamous cell carcinoma

Table 3 Incidence rate of skin cancer in lung vs. liver transplant recipients

Recipients	Lung	Liver	P value[a]
All	0.024 (SD 0.54)	0.006 (SD 0.04)	< 0.001
Caucasian only	0.03 (SD 0.058)	0.01 (SD 0.05)	0.002
Non-Caucasian only	0.01 (SD 0.05)	0.003 (SD 0.03)	0.04

SD standard deviation

[a]Conducted using the Kruskal–Wallis test for non-parametric comparison

Caucasian lung transplant recipients than Caucasian liver transplant recipients (0.03 vs. 0.01 per year, $p=0.02$) (Table 3). In addition, despite the significantly lower incidence in non-Caucasian transplant patients, they also had a higher annual incidence rate of skin cancer in lung vs. liver transplant recipients (0.01 vs. 0.003 per year, $p=0.04$) (Table 3).

The standard immunosuppressive regimens were similar between lung and liver transplant recipients at our institution during the study period and included tacrolimus and mycophenolate mofetil, and often prednisone, as well as initial prophylaxis with sulfamethoxazole-trimethoprim and valganciclovir. Mycophenolate treatment was maintained throughout the course in lung transplant recipients, whereas this agent was weaned in liver transplant patients. Mycophenolate was discontinued in approximately 50% of liver transplant recipients after 1 year and in 75% 2 years after transplant. There was an additional identified difference: lung transplant, but not liver transplant, recipients routinely received voriconazole as aspergillosis prophylaxis during the years examined in the study.

4 Discussion

The primary results of this study demonstrate a significantly increased risk of skin cancer, particularly SCC, development in Caucasian organ transplant recipients compared with their non-Caucasian counterparts. This is in accordance with the results of several other large studies suggesting that skin of color in transplant patients confers lower risk [8–10]. For instance, in a study of 91 lung transplant recipients by Zwald et al., a multivariate analysis demonstrated that Fitzpatrick Skin Types I and II were independent risk factors for skin cancer development, and conversely a darker skin type (Fitzpatrick Skin Types V or VI) was a protective factor [9]. Corresponding findings have also been reported when considering patient race instead of skin type. Garrett et al. conducted a study of 496,951 organ transplant recipients in USA from 1987 to 2013 and reported significantly higher rates of post-transplant skin cancer among white patients compared with those identifying as Black, Hispanic, Asian, American Indian, or Pacific Islander [10].

The incidence of SCC development exceeded that of BCC or melanoma in our study, in accordance with the well-documented finding that SCC predominates post-transplantation. The disproportionate risk of SCC has been attributed to an impaired immune response to oncogenic virus exposure in the context of prolonged immunosuppression, mechanisms related to inadequate DNA repair, or other genetic factors [1, 3]. The central role of human papilloma virus has been strongly suggested by the observation that human papilloma virus DNA is present in up to 90% of SCCs in transplant patients [1, 11].

The substantially higher risk identified in Caucasian compared with non-Caucasian transplant recipients presumably relates to increased susceptibility to UV-induced damage.

The increased pigmentation in non-Caucasians is protective against UV absorption, thereby reducing UV damage. It has been previously reported that cumulative lifetime UV exposure and residence in a region with high sunlight exposure are independent risk factors for the development of SCC after transplantation [9, 12]. The effect of sun exposure in post-transplant SCC may interact with other oncogenic mechanisms. For example, Hufbauer and colleagues demonstrated in mouse models that cells expressing human papilloma virus-associated E6 proteins were significantly less effective at detecting and repairing UV-induced DNA damage [11].

We found that lung transplant recipients are at significantly higher risk of skin cancer development when compared with liver transplant patients. This trend was observed despite the fact that, in our cohort, on average, lung transplant patients were younger and included a higher proportion of female individuals, both factors previously shown to be protective against skin cancer development [13, 14]. The proportion of Caucasian individuals within our lung transplant population was significantly higher than in the liver transplant group. Therefore, sub-analyses were performed restricted to either Caucasian or non-Caucasian patients, which confirmed the elevated risk associated with lung transplantation in both groups, despite the significantly reduced incidence in non-Caucasians.

Several studies have previously reported a particularly high risk of skin cancer associated with lung transplantation [14–16]. For example, in a study by Rashtak et al., the authors reported that the incidence of skin cancer among lung transplant recipients exceeded that of both heart transplant and pancreas transplant recipients [14]. In another large study of the Swedish transplant registry, the risk of skin cancer was significantly higher in lung transplant patients compared with kidney or liver transplant recipients. This has been previously proposed to be the result of the extent of immunosuppression required, rather than the indication for transplantation or comorbidities [15].

In our comparison, at the Keck University of South California, the immunosuppressive regimens were similar between lung and liver transplant recipients. An exception was that mycophenolate was maintained in lung transplant recipients throughout but tapered in liver transplant patients. In addition, during the study period, lung transplant patients received voriconazole for aspergillus prophylaxis.

Voriconazole was approved in 2002 for the treatment of aspergillosis, candidiasis, scedosporium, and fusarium species, and was commonly used for prophylaxis in lung transplant recipients. Recently, a number of studies have suggested that long-term exposure to voriconazole may contribute to the increased risk of SCC in lung transplant patients compared with other transplanted organs [9, 12, 17–21]. In a multicenter retrospective cohort study of 921 lung transplant patients, exposure to voriconazole was associated with a hazard ratio of 2.4 for the development of SCC, after adjustment for confounding factors, which included controlling for specific immunosuppressant agents [19]. Similarly, Feist et al. reported that lung transplant recipients exposed to voriconazole demonstrated nearly a threefold higher odds of developing SCC in multivariable logistic regression models [7]. In a study by Singer and colleagues, a dose-dependent increased risk of SCC was reported in lung transplant patients taking voriconazole, which correlated to a 28% increase in the absolute risk of SCC after 5 years [21].

Voriconazole has been reported to cause photosensitivity with increased susceptibility to sunburns, photoaging, and other phototoxic reactions [7, 12, 17]. The association between voriconazole and cutaneous malignancy is thought to relate to the photosensitizing properties of voriconazole, which may accelerate the consequences of UV damage, especially in the context of immunosuppression [12, 17]. Voriconazole has been implicated in promoting the development of actinic keratosis and SCC in the general population, as well as in contributing to development of melanoma in a case series of five patients receiving long-term voriconazole therapy [18, 22]. The mechanisms through which voriconazole may promote skin cancer development are not well understood. It has been hypothesized that the main N-oxide metabolite of voriconazole may produce phototoxicity as a result of increased photoabsorption within the UVA and UVB ranges. Additionally, voriconazole-induced alterations in retinoid metabolism, leading to a build-up of phototoxic retinoids, have also been suggested [12, 14, 17, 18, 22]. To be comprehensive, there are other studies that have challenged the association between voriconazole and skin cancer risk in transplant patients after controlling for other factors such as sun exposure and comorbid conditions [13, 14].

Notably, several recent studies have demonstrated that azathioprine, likely secondary to its photosensitizing properties, elevates the risk of skin cancer more significantly than other immunosuppressive agents in both organ transplant recipients and patients with inflammatory bowel disease [23–25]. For example, Cho and colleagues recently reported a significantly elevated risk of both BCC and SCC in association with exposure to azathioprine [23]. In multivariate analysis, azathioprine was associated with significantly higher risk than mycophenolate mofetil, sirolimus, cyclosporine, or tacrolimus, and the authors proposed that this increased risk was due to the known photosensitizing properties of azathioprine [23]. The role of photosensitivity in the association between azathioprine and keratinocyte skin cancer is supported by another study in patients with inflammatory bowel disease, which reported an increased risk of keratinocyte skin cancer in Caucasian patients exposed to azathioprine, but not in patients of other racial backgrounds associated with darker phototypes [25].

A notable strength of this study was the inclusion of a large, racially diverse sample population. However, we also wish to note possible limitations. Patients in our cohort were classified by self-reported race, as records only very rarely noted Fitzpatrick Skin Types, and therefore, the categories available could be imperfect reflections of skin types. Although the review of patient records was thorough and extensive, it is reasonable to conclude an underreporting of skin cancer incidence, as patients may have also received follow-up care from outside institutions not perfectly captured in requested transfers of information. Additionally, the exclusion of patients who did not survive for the entire observation period could potentially introduce a source of bias. Conversely, the limitation to surviving patients allowed for a more accurate capture of skin cancer events, given the high early mortality rates. Finally, our institution is located in Los Angeles where there are approximately 284 days of sunshine every year, certainly more than in most other geographic areas, thus accentuating the importance of photosensitivity in our population.

5 Conclusion

Caucasian patients demonstrate a significantly elevated risk of post-transplantation SCC compared with non-Caucasian patients. Lung transplant recipients demonstrate a significantly higher rate of skin cancer compared with liver transplant patients, irrespective of race, which may relate to greater exposure to immunosuppressive agents, as well as to voriconazole, a known photosensitizing agent, among lung transplant recipients. These results suggest that susceptibility to UV radiation owing to a fair skin type and, additionally, exposure to photosensitizing drugs, are important factors in the association between organ transplant and skin cancer. While organ transplantation and immunosuppression are associated with high rates of skin cancer, patients with a Caucasian background and those exposed to photosensitizing agents may be at particularly elevated risk. We suggest that there should be increased attention to possible effects of various transplant regimens on susceptibility to skin cancer.

Acknowledgements The authors acknowledge Griselda Hagmaier, MBA, MHA for administrative support in the process of obtaining study approval. Findings of this study have been presented in part at the American Academy of Dermatology 2018 annual meeting in San Diego, California by Cohen et al. and Krivitskiy et al.

Compliance with Ethical Standards

Funding No sources of funding were received for the preparation of this article.

Conflict of interest Brandon E. Cohen, Igor Krivitskiy, Sarah Bui, Kevin Forrester, Jeffrey Kahn, Richard Barbers, and Binh Ngo have no conflicts of interest that are directly relevant to the contents of this article.

Ethics approval The Institutional Review Board of the University of Southern California approved this study.

Consent to participate Informed consent was not obtained because of the retrospective nature of this study and the determination of lack of potential harm to subjects.

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