
Fitzpatrick skin phototype is an independent predictor of squamous cell carcinoma risk after solid organ transplantation

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Background: Solid organ transplant recipients (OTR) are at an increased risk of developing squamous cell carcinoma (SCC) of the skin after transplantation. In predominantly white cohorts, Fitzpatrick skin type (FST) has been reported to be a risk factor for developing posttransplantation skin cancers.

Objective: Our goal was to determine if FST is a statistically significant risk factor for the development of SCC after solid organ transplantation in a diverse US population of OTR.

Methods: A cohort of OTR completed a questionnaire of demographic factors, transplant type, FST, and skin cancer history. Univariate and multivariate analyses were performed to determine the risk factors for development of SCC after transplantation.

Results: As expected, male subjects had an increased risk for SCC compared with female subjects ($P = .02$), and those aged 50 years and older at the time of transplantation were more likely to develop SCC compared with those younger than 50 years ($P < .001$). The risk of SCC increased with each incremental decrease in FST, from FST VI to FST I (linear test for trend $P < .001$).

Limitations: Our questionnaire did not ask specifically about immunosuppressive medications; instead, organ transplant category was used as a proxy for level of immunosuppression.

Conclusions: FST, a patient-reported variable, is an independent risk factor for the development of SCC in OTR, and should be elicited from patients who have gone or will undergo organ transplantation. (J Am Acad Dermatol 2013;68:585-91.)

Key words: Fitzpatrick skin type; immunosuppression; organ transplant recipient; phototype; solid organ transplantation; squamous cell carcinoma.

Currently, there are approximately 140,000 organ transplant recipients (OTR) in the United States.¹ The risk of systemic and cutaneous cancers is increased within this population, with the most common posttransplantation neoplasm being nonmelanoma skin cancers (NMSC). Most studies have shown a predominance

Abbreviations used:

CI:	confidence interval
FST:	Fitzpatrick skin type
HR:	hazard ratio
NMSC:	nonmelanoma skin cancer
OTR:	organ transplant recipients
SCC:	squamous cell carcinoma

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of squamous cell carcinomas (SCC) over basal cell carcinomas in OTR, in contrast to the general population.¹⁻³ In addition to the increased incidence with which they occur, these tumors behave more aggressively in the posttransplantation population, with a metastatic rate as high as 8% and 3-year mortality of up to 46%.^{2,4,5} Current recommendations call for annual full-body skin examination for all OTR, although the risk for skin cancer is believed to be lower for OTR with darker skin.⁶

Originally developed to assist in the determination of the minimal erythema dose in white patients undergoing light therapy, Fitzpatrick skin type (FST) has since been more broadly used by dermatologists as a measure of sun sensitivity and skin cancer risk.^{7,8} A 6-point categorical scale is used to describe a patient's history of tanning ability and tendency to burn. Much of the data regarding posttransplantation skin cancer has been obtained from cohorts of OTR in northern Europe and Australia that are predominantly or exclusively white.^{5,9,10} Nonetheless, some analysis regarding the connection between skin color or phototype and development of skin cancer has been performed: whites have been noted to have an odds ratio of 12 for SCC occurrence when compared with non-whites, FST of I or II was found to be a significant risk factor (when compared with skin type III or IV) in liver OTR, and Irish renal OTR who later developed NMSC disproportionately had type I skin.^{4,5,11} Type II skin has been reported to be a significant risk factor for the development of skin cancers, with patients of FST III to V enjoying an 83% risk reduction.¹²⁻¹⁴ Larger studies have revealed an increased risk of developing keratotic lesions in patients with lighter skin types, although that comparison did not use the Fitzpatrick phototype system and instead used descriptions such as "medium," "fair," and "olive" skin types.¹⁵

To date, the data regarding FST and skin cancer risk have been drawn from relatively homogeneous cohorts. Previous studies have not evaluated the incremental risk of each FST for the development of SCC after transplantation within a diverse, admixed US population. Because of the significant morbidity and mortality associated with skin cancer after solid organ

transplantation, it is imperative to identify clinically relevant risk factors for the development of skin cancers in the OTR so that appropriate monitoring and education programs can be put in place. We analyzed a cohort of US OTR to determine whether FST predicts the risk of SCC after transplantation.

METHODS

Sample

In all, 694 OTR were enrolled in the study between 2004 and 2008 via physician contact and direct patient advertisement. Patients were recruited through physician contact, magazine advertisements, a booth at the Transplant Games, and direct mailings to patients via transplantation organizations. Physicians were recruited to refer patients through advertisements in transplantation and dermatology journals and through direct mailings to members of professional dermatology organizations. Subjects who opted to con-

tact the study coordinators were enrolled in person, by mail, or by telephone. All subjects provided informed consent according to the procedures approved by the University of California, San Francisco Committee on Human Research and adherent to the Declaration of Helsinki Principles.

Data collection and measures

Each subject completed a questionnaire that gathered data on sex, age, age at transplantation, race, FST (description of tendency to burn or tan), hair color, eye color, time since transplantation, type of organ transplanted, and self-reported history of any skin cancer.⁷ Enrolled subjects were asked to consent to collection and review of medical records relevant to skin cancer. All reports of skin cancer diagnoses and dates of diagnoses were confirmed by review of pathology report.

FST, the primary predictor, was measured on a 6-point categorical scale according to the patient's response to the question "How does your skin react if you go outside without sunscreen?" Answer choices were: (I) always burns easily, never tans; (II) always burns easily, tans a little; (III) burns moderately, tans gradually; (IV) burns a little, always tans well; (V) rarely burns, tans profusely; and (VI) never burns. Secondary predictors were measured as

CAPSULE SUMMARY

- Solid organ transplant recipients have a significantly higher risk of developing nonmelanoma skin cancers, especially squamous cell carcinomas.
- In this study, Fitzpatrick skin type was a significant risk factor for the development of squamous cell carcinomas in a diverse posttransplantation US population.
- The findings of advancing age, male sex, and Fitzpatrick skin type as risk factors can be generalized to a broader US posttransplantation population and should guide skin cancer surveillance and education.

follows: race (select as many as apply) of white, black/African American, Asian, Hispanic or Latino, American Indian/Alaskan Native, and Hawaiian or Pacific Islander; hair color (select one) of black, brown, blonde, or red; and eye color (select one) of brown, hazel, blue, or other (write in).

For analysis, age at transplantation was dichotomized into age younger than 50 years and 50 years or older. Eye color was dichotomized into brown/hazel and blue/gray/green, and hair color was dichotomized into brown/black and red/blonde. Transplanted organ was categorized as thoracic (heart, lung, heart-lung, and heart-kidney) or abdominal (kidney, liver, and pancreas).

Statistical analysis

Variables were analyzed with 2-sided Fisher exact test or 2-sample Wilcoxon rank sum test. We assessed correlations between all potential predictors, with correlation coefficients $<|0.35|$ in all cases (-0.09 to 0.33).

A pathological confirmation of skin cancer history was obtained for 556 subjects (80.1%); 138 subjects either did not consent to record review or their records were unobtainable. The subjects with missing data were similar with respect to age, sex, organ transplanted, FST, hair and eye color, and race but were older and more likely to have reported a history of skin cancer than those with complete data. We therefore generated inverse weights to address potential bias in survey response and data collection.^{16,17} Inverse weights were based on a logistic regression model of missingness on sex, age at transplantation, and reported history of skin cancer. These weights were incorporated when the data were declared to be survival-time data.

We used Cox proportional hazard models to assess the incremental impact of FST on the risk of developing SCC. FST was modeled as a 6-level categorical variable. Variables were selected by a modified Allan-Cady backward selection procedure. Gender and age at transplantation were included in the Cox models a priori based on known associations with skin cancer after organ transplantation.¹ Type of organ transplanted was included to adjust for level of immunosuppression (higher in thoracic OTR than abdominal OTR).

We next performed binary tests of interaction between all predictors, which revealed interactions between race and FST as well as between race and organ transplanted. Further, we identified that 98% of SCC developed in white subjects. Because of these interactions and the rarity of SCC development in nonwhite subjects, models were stratified by race (white/nonwhite).

The proportionality of hazards assumption was tested and confirmed with the Schoenfeld test. The goodness of fit of the models was confirmed by comparing a plot of the Cox-Snell residuals with the Nelson-Aalen cumulative hazard function.

The impact of hair color and eye color on FST was measured by ordinal logistic regression.

RESULTS

In all, 694 OTR completed the survey, 449 male and 245 female (Table D). A total of 587 subjects had received an abdominal organ transplantation and 107 had received a thoracic organ transplantation. In all, 384 patients were transplanted before the age of 50 years whereas 299 were transplanted after age 50 years. A total of 639 subjects self-identified as white. All 6 FSTs were represented in both white and nonwhite groups.

Among the 556 patients for whom skin cancer history confirmation was obtained, 317 (57%) had a history of SCC (Table II). The mean age at the time of transplantation for the subset that developed an SCC was 47.7 years, compared with 44.5 years for the unaffected group. Univariate analysis revealed a significantly increased risk in male individuals, thoracic OTR, those who self-identified as white, and subjects who were older than age 50 years at the time of transplantation. Hair color and eye color ($P = .8$ and $P = .08$, respectively) were not univariate predictors of SCC development. The mean duration of follow-up was 9.9 years for subjects with SCC and 10 years for subjects with no history of SCC ($P = .6$).

The final multivariate model included FST adjusted for sex, age at transplantation, and organ transplanted (Table III). The risk of SCC increased with each incremental decrease in FST (linear test for trend $P < .001$), such that subjects with type I skin had a 1.7-fold increased risk for SCC over those with type IV skin (hazard ratio [HR] 1.67, 95% confidence interval [CI] 1.07-2.62, $P = .02$) and a 3.5-fold increased risk over those with type VI skin (HR 3.47, 95% CI 1.46-8.28, $P = .005$) (Fig 1).

The overall 5-, 10-, and 15-year cumulative incidence of SCC after transplantation was 20%, 45%, and 59% (Table IV). Fair skin types had a higher incidence of SCC than the overall population, whereas darker skin types had a lower incidence. The cumulative incidence of SCC at 10 years ranged from 51% in patients with type I skin to 8% in subjects with type VI skin.

Male subjects had a 1.3-fold increased risk for SCC compared with female subjects (HR 1.33, 95% CI 1.04-1.71, $P = .02$), and subjects age 50 years and older at the time of transplantation had a 4.3-fold increased risk for SCC compared with those younger than 50 years (HR 4.34, 95% CI 3.23-5.83, $P < .001$).

Table 1. Characteristics

Sex	
Male	449 (64.7)
Female	245 (35.3)
Organ category	
Kidney, liver, pancreas	587 (84.6)
Heart, lung (including kidney)	107 (15.4)
Fitzpatrick skin type	
I: Always burns easily	53 (7.6)
II: Always burns easily, tans little	134 (19.3)
III: Burns moderately, tans gradually	195 (28.1)
IV: Burns a little, tans well	188 (27.1)
V: Rarely burns, tans profusely	80 (11.5)
VI: Never burns	24 (3.5)
Race	
White	639 (92.1)
Black/African American	11 (1.6)
Hispanic/Latino	26 (3.8)
Asian	1 (0.1)
American Indian/Alaskan Native	3 (0.4)
>1 Race reported	6 (0.9)
Eye color	
Brown	213 (30.7)
Hazel	136 (19.6)
Green	25 (3.6)
Blue/gray	301 (43.4)
Hair color	
Black	72 (10.4)
Brown	445 (64.1)
Blonde	124 (17.9)
Red	34 (4.9)
Age at time of transplantation, y	46.9 ± 14.1
<50	384 (55.3)
≥ 50	299 (43.1)

Data presented as n (%) or mean ± SD. n = 694.

Categories may not total to 694 because of missing data points.

There was a trend toward higher risk in thoracic OTR compared with abdominal OTR, but this did not achieve statistical significance (HR 1.32, 95% CI 0.95-1.83, $P = .09$). As pancreatic OTR receive higher levels of immunosuppression than other abdominal OTR, we ran a sensitivity analysis of the model in which the 21 patients with pancreas transplantations were reclassified as thoracic. There were no qualitative changes in the model results, but the observed HR for thoracic/pancreas compared with kidney/liver was 1.43 (99% CI 1.05-1.94, $P = .022$).

Hair color and eye color were not associated with risk for SCC on univariate analysis and were removed from the final multivariate model during backward selection. Both hair color and eye color were predictive of FST by ordinal logistic regression ($P < .001$ for hair color; $P = .001$ for eye color), suggesting an association of these variables with tanning ability. Notably, this finding was driven by white subjects in

the population, as hair and eye color did not predict FST in the nonwhite subgroup ($P = .9$ for hair color; $P = .2$ for eye color).

DISCUSSION

The objective of this study was to determine if FST is an independent risk factor for the development of SCC after solid organ transplantation in a diverse US population. The development of SCC was a common occurrence in our cohort of OTR. Approximately 43% of subjects developed an SCC by 10 years after transplantation. Notably, 72% of patients who received a thoracic organ transplantation developed an SCC by 10 years after transplantation, a markedly higher rate than reported in previous studies.⁵

FST was an important predictor of SCC development in our cohort, particularly when comparing patients with skin types I, II, or III to those of skin type VI. Early studies on the predictive effect of FST in NMSC found that among patients treated with psoralen plus ultraviolet A, the risk of NMSC was significantly higher in skin types I and II compared to patients with skin type IV. However, that cohort comprised patients with psoriasis receiving ultraviolet therapy and included a 4-point, rather than the full 6-point, FST scale.¹⁸ Previous studies looking at the relationship of skin color or FST with skin cancer in OTR have been limited by the fact that their cohorts were drawn from more homogeneous populations in Europe and Australia.⁵⁻⁷ Few studies have had cohorts that include all 6 FST, and those that do have few patients with skin type V or VI.^{14,19} Other studies that have looked at the predictive value of phenotypic characteristics on risk of skin cancer found an association only in populations with red hair, blue eyes, and highly freckled skin.²⁰ Interestingly, in our cohort, hair color and eye color were not significant risk factors for SCC development in multivariate analysis, although they did predict FST in the subset of white patients ($P < .001$ and $P = .001$, respectively). Our results also confirm data from previous studies on risk for SCC after transplantation. Male sex and advanced age at time of transplantation were found to be significant risk factors as well, with male subjects more likely to develop SCCs than female subjects and with patients 50 years of age or older at the time of transplantation developing SCCs at a higher rate than younger OTR. These had previously been described as risk factors within the northern European and Australian cohorts studied.^{10,12-14,19,21} The increased risk with advancing age may be attributable to increased cumulative sun exposure before transplantation.¹² Ultraviolet radiation is thought to play a major role in the pathogenesis of NMSC, and in posttransplantation patients the vast

Table II. Subjects with complete skin cancer data (n = 556)

	Developed SCC n = 317	No SCC n = 239	P value
Sex			
Male	226 (62.4)	136 (37.6)	<.001
Female	91 (46.9)	103 (53.1)	
Organ category			
Kidney, liver, pancreas	251 (52.9)	223 (47.1)	<.001
Heart, lung (including kidney)	66 (80.5)	16 (19.5)	
Fitzpatrick skin type			
I: Always burns easily	29 (67.4)	14 (32.6)	<.001
II: Always burns easily, tans little	70 (64.2)	39 (35.8)	
III: Burns moderately, tans gradually	105 (68.2)	49 (31.8)	
IV: Burns a little, tans well	77 (51.7)	72 (48.3)	
V: Rarely burns, tans profusely	25 (40.3)	37 (59.7)	
VI: Never burns	5 (21.7)	18 (78.3)	
Race			
White	309 (60.1)	197 (38.9)	<.001 (white vs nonwhite)
Nonwhite	7 (16.7)	35 (83.3)	
Black/African American	0 (0)	11 (100)	
Hispanic/Latino	4 (16)	21 (84)	
Asian	0 (0)	1 (100)	
American Indian/Alaskan Native	0 (0)	2 (100)	
>1 Race reported	3 (100)	0 (0)	
Eye color			
Brown/hazel	150 (54.2)	127 (45.8)	.08
Blue/gray/green	161 (61.7)	100 (38.3)	
Hair color			
Brown/black	245 (58.6)	173 (41.4)	.8
Red/blonde	71 (57.3)	53 (42.7)	
Age at time of transplantation, y	47.7 ± 14.5	44.5 ± 13.6	.002
<50	166 (51.7)	155 (48.3)	
≥ 50	149 (65.4)	79 (34.6)	
Time to event, y	9.9 ± 8.3	10 ± 7.5	

Data presented as n (%) or mean ± SD.

P value by Fisher exact test or Wilcoxon rank sum.

Categories may not total to 556 because of missing data points.

SCC, Squamous cell carcinoma.

majority of NMSC are seen in sun-exposed sites.^{4,11} Many previous studies have noted an increased risk of SCC in thoracic OTR. In our cohort, a trend toward higher risk of SCC in thoracic OTR when compared with abdominal OTR was noted, but significance was not achieved. We performed a power calculation to assess whether our inability to achieve statistical significance between thoracic and abdominal subjects was a result of small sample size. Given the event rate of 0.57 in our study, we would need a sample size of 715 patients to detect the observed HR of 1.32 between thoracic and abdominal subjects. Therefore we are likely underpowered to achieve statistical significance in our study. It is possible that the inclusion of pancreatic OTR in the abdominal organ group biases the HR toward the mean, as these patients typically require higher levels of immunosuppression than kidney and liver OTR. Of the 556

subjects with confirmed pathology, there were 474 abdominal OTR, 18 of whom (4%) had a pancreas transplantation (primarily kidney/pancreas). The sensitivity analysis of the model with pancreas OTR reclassified in the thoracic transplantation category suggests that the higher level of immunosuppression required after pancreatic transplantation increases the risk for SCC and that increased immunosuppression increases the risk for SCC, similar to previous reports. Notably, the sample size required to detect a HR of 1.43 is 431, well within our cohort size of 556. Therefore we are confident that our model is robust to adjustment for transplanted organ as a marker for level of immunosuppression.

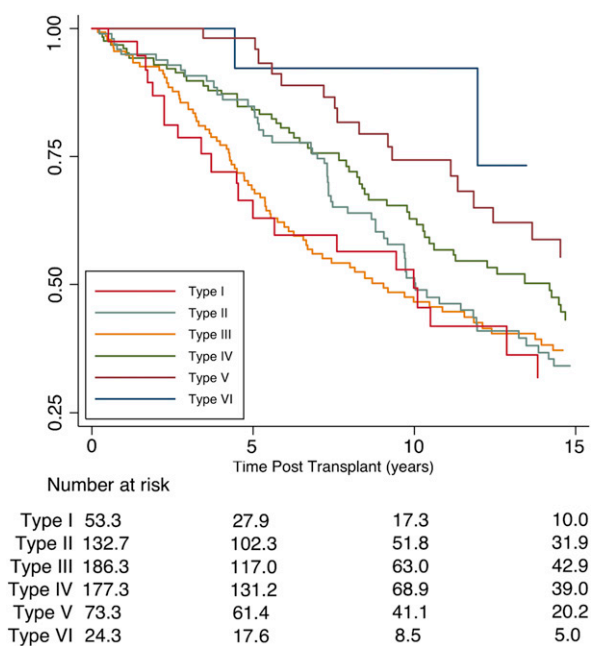
Notably, because this study examined the risk factors associated with skin cancer development in a large cohort of US OTR of diverse FST and both abdominal and thoracic organ transplantations, its

Table III. Relative risk of developing squamous cell carcinoma (hazard ratios) based on Fitzpatrick skin type

	Hazard ratio*	95% CI	P value
Fitzpatrick skin type			
I	3.47	1.46-8.28	.01
II	2.63	1.16-5.92	.02
III	2.79	1.24-6.30	.01
IV	2.07	0.91-4.70	.08
V	1.58	0.66-3.81	.3
Male sex	1.33	1.04-1.71	.02
Age \geq 50 y at transplantation	4.34	3.24-5.83	<.001
Thoracic organ transplantation	1.32	0.96-1.83	.09

CI, Confidence interval.

*Hazard ratio of >1.0 represents greater risk for developing squamous cell carcinoma for subjects with given Fitzpatrick skin type relative to those with Fitzpatrick skin type VI. Linear test for trend $P = .0006$. Models were stratified by race (white vs nonwhite).

**Fig 1.** Squamous cell carcinoma-free survival after organ transplantation by Fitzpatrick skin type.

findings can be generalized to a broader US post-transplantation population. Our population breakdown was similar in gender, age, and transplanted organ to the US transplantation population during the period studied based on Organ Procurement and Transplantation Network data. Although diverse with regard to FST, our population predominantly self-identified as white.

In addition, the confirmation of reported skin cancer history with pathology review decreased the possibility of recall bias in this observational study.

Table IV. Cumulative incidence of squamous cell carcinoma by Fitzpatrick skin type

	5-y	10-y	15-y
Overall	0.20	0.43	0.59
I. Always burns easily, never tans	0.37	0.51	0.68
II. Always burns easily, tans a little	0.15	0.49	0.66
III. Burns moderately, tans gradually	0.31	0.53	0.63
IV. Burns a little, always tans well	0.16	0.37	0.57
V. Rarely burns, tans profusely	0.02	0.26	0.45
VI. Never burns	0.08	0.08	0.27

We have previously described a correct classification rate of 0.83 for self-report of SCC in this cohort.²² Although our questionnaire did not ask specifically about immunosuppressive medications, organ transplant category was used as a proxy for level of immunosuppression.^{6,23-27} Further studies may examine why no significant difference in risk was seen between the organ transplant categories. We collected data regarding race, hair color, eye color, and FST, but did not obtain skin color. Future studies are needed to determine the relative predictive value of constitutive skin color versus tanning ability in determining skin cancer risk.

This study demonstrates that FST, age at time of transplantation, and male sex are independent risk factors for the development of SCC in the posttransplantation population. In our experience, clinicians often assign a FST to patients during the physical examination based on race and pigmentary phenotype; it is important to remember that FST is a patient-reported variable not determined by clinical examination. Notably, within the group self-identifying as white there were subjects who reported burning and tanning histories consistent with each FST. Ultimately, the significantly increased risk of SCC based on FST should compel dermatologists to use this measure rather than race to risk-stratify patients who have undergone, or will undergo, solid organ transplantation. Until a clinical predictive model is validated in a prospective study, male OTR, patients who receive a transplantation at or after age 50 years, and those with a burning and tanning history consistent with FST I, II, or III should receive significant education and aggressive surveillance for the development of skin cancers.

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