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Incidence of and Risk Factors for Skin Cancer in Organ Transplant Recipients in the United States

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IMPORTANCE Skin cancer is the most common malignancy occurring after organ transplantation. Although previous research has reported an increased risk of skin cancer in solid organ transplant recipients (OTRs), no study has estimated the posttransplant population-based incidence in the United States.

OBJECTIVE To determine the incidence and evaluate the risk factors for posttransplant skin cancer, including squamous cell carcinoma (SCC), melanoma (MM), and Merkel cell carcinoma (MCC) in a cohort of US OTRs receiving a primary organ transplant in 2003 or 2008.

DESIGN, SETTING, AND PARTICIPANTS This multicenter retrospective cohort study examined 10 649 adult recipients of a primary transplant performed at 26 centers across the United States in the Transplant Skin Cancer Network during 1 of 2 calendar years (either 2003 or 2008) identified through the Organ Procurement and Transplantation Network (OPTN) database. Recipients of all organs except intestine were included, and the follow-up periods were 5 and 10 years.

MAIN OUTCOMES AND MEASURES Incident skin cancer was determined through detailed medical record review. Data on predictors were obtained from the OPTN database. The incidence rates for posttransplant skin cancer overall and for SCC, MM, and MCC were calculated per 100 000 person-years. Potential risk factors for posttransplant skin cancer were tested using multivariate Cox regression analysis to yield adjusted hazard ratios (HR).

RESULTS Overall, 10 649 organ transplant recipients (mean [SD] age, 51 [12] years; 3873 women [36%] and 6776 men [64%]) contributed 59 923 years of follow-up. The incidence rates for posttransplant skin cancer was 1437 per 100 000 person-years. Specific subtype rates for SCC, MM, and MCC were 812, 75, and 2 per 100 000 person-years, respectively. Statistically significant risk factors for posttransplant skin cancer included pretransplant skin cancer (HR, 4.69; 95% CI, 3.26-6.73), male sex (HR, 1.56; 95% CI, 1.34-1.81), white race (HR, 9.04; 95% CI, 6.20-13.18), age at transplant 50 years or older (HR, 2.77; 95% CI, 2.20-3.48), and being transplanted in 2008 vs 2003 (HR, 1.53; 95% CI, 1.22-1.94).

CONCLUSIONS AND RELEVANCE Posttransplant skin cancer is common, with elevated risk imparted by increased age, white race, male sex, and thoracic organ transplantation. A temporal cohort effect was present. Understanding the risk factors and trends in posttransplant skin cancer is fundamental to targeted screening and prevention in this population.

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Supplemental content

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The number of solid organ transplants performed in the United States is increasing. In 1988, 12 623 transplants were carried out nationwide; by 2015 this number has increased nearly 3-fold to 30 969.[1] The lifelong immunosuppressive regimes required to preserve graft function place organ transplant recipients (OTRs) at increased risk of skin cancer, the most common tumor in this population.[2-4] The risk of skin cancer is higher in OTRs than in the general population, 65-fold for cutaneous squamous cell carcinoma (SCC) and 3-fold for malignant melanoma (MM).[3-6] A number of risk factors for posttransplant skin cancer have been identified in single-center studies: being male,[7,8] white,[9-11] 50 years or older at the time of transplant,[6,7,12] a recipient of a thoracic organ,[5,13] and having a longer time elapsed since transplant.[13] A history of pretransplant treated skin cancer,[14,15] as well as past overexposure to ultraviolet (UV) radiation[16-18] are also believed to increase the risk of posttransplant skin cancer.

Multiple studies have highlighted the increasing problem of skin cancer in OTRs, though data are limited in key aspects. Although single-center studies have been published, incidence data across a wider transplant population are lacking. For example, Brewer et al[7] found 0.43 skin cancers per patient per year (or 430 per 1000 patient-years) in a cohort of 312 heart transplant recipients seen at the Mayo Clinic, while Esfeh et al[19] observed 84.8 skin cancer cases per 1000 person-years in a cohort of 998 liver transplant recipients at the Cleveland Clinic. Altogether, data for skin cancer among pancreas,[20,21] liver,[19,22] heart,[7,23] and lung[12] transplant recipients are limited, while incidence of skin cancer in kidney transplant has been a focus of studies.[4,16,17,21,24-27] Thus, there is a need for reliable data estimating the incidence of skin cancer across all organ transplant types and subsuming a range of recognized risk cofactors. In this study, we combined national transplant registry data with skin cancer outcomes review to estimate a US population-based incidence of skin cancer and model risk associated with known or suspected risk factors for disease.

Key Points

Question What is the population-based incidence of posttransplant skin cancer in the United States?

Findings In this population-based cohort study of 10 649 organ transplant recipients, the incidence ratio for posttransplant skin cancer overall was 1437 per 100 000 person-years. The specific subtype rates for squamous cell carcinoma, malignant melanoma, and Merkel cell carcinoma were 812, 75, and 2 per 100 000 person-years, respectively.

Meaning Posttransplant skin cancer is common, with elevated risk imparted by specific risk factors.

Methods

Transplant Skin Cancer Network

The Transplant Skin Cancer Network (TSCN) is led by the University of California, San Francisco, and includes 26 US transplant centers with an active collaboration between the dermatology and transplant services (eTable 1 in the Supplement). Participation in the TSCN was open to all transplant centers in the United States; 26 centers elected to participate in this network study based on access to registry and medical records and ethics approval for a multicenter study. The study was approved by the Committee on Human Research at the University of California, San Francisco, as well as at each participating center.

Study Population

Adult (≥18 years) recipients of a primary transplant performed at participating transplant centers either between January 1 through December 31, 2003, or between January 1 through December 31, 2008, were eligible for inclusion. The 2 years studied were selected to enable a 5-year and 10-year follow-up period to investigate differences in transplant cohorts between 2003 and 2008 and to capture changes in immunosuppressant regimes introduced between the 2 time periods, as well as other temporal trends. Transplanted organs included the lung, heart (either organ or heart-lung, referred to here as "thoracic" transplants), pancreas, liver, and kidney; intestinal transplants were excluded given the small number (n = 36) and limited centers.

Eligible subjects were identified using the Standard Transplant Analysis and Research (STAR) file, based on Organ Procurement Transplant Network (OPTN) data as of December 2013. The OPTN database contains pretransplant and posttransplant data on every transplant event occurring in the United States since 1987; data are reported to the OPTN by transplant centers. Using the OPTN database, the demographics of our 26-center cohort were compared to those of all US recipients transplanted in either 2003 or 2008.

Measurements

Outcome Variables

The primary study outcome was time until diagnosis of any skin cancer and, separately, SCC, MM, or Merkel cell carcinoma (MCC) from the date of transplant. Outcome data were obtained from review of medical, transplant, dermatology, dermatopathology, and specialty records (otolaryngology, surgical oncology, radiation oncology, hematology-oncology). Written guidance on reviewing medical records and adjudicating outcomes was distributed by the lead center. Skin cancer was captured by the presence of a documented positive history. Skin cancer history was considered negative if it was documented as negative in the medical records or if a detailed medical history did not record any mention of skin cancer. Skin cancer history could not be determined and was marked as "missing" if there was no detailed general medical or dermatological history documented. Dates were entered in an electronic database (generated with REDCap software) in month-day-year format. If the day was not known, the first day of the month was entered. If only the year was known, January 1 of the year was entered.

Predictor Variables

Predictor variables drawn from the STAR file included sex,[7,8] race,[9-11] age at transplant,[6,7,12] organ transplanted,[5,13] year of transplant,[13] and residential zip code at the time of transplantation.[16-18] History of pretransplant skin cancer was

established from record review. Predictors were selected based on previous research showing an effect on posttransplant skin cancer. MapQuest Open geocoding software (MapQuest Inc) was used to convert the zip code at the time of transplant into latitude coordinates, which were used as a proxy for pretransplant UV exposure.[28,29]

Statistical Analysis

The incidence rate (IR) of skin cancer, SCC, MM, and MCC was calculated per 100 000 person-years of observation. Patients were followed from the date of transplant until the earliest of skin cancer, death, or last follow-up. If the date of diagnosis was not known (n = 120), the date of last follow-up, obtained from the medical record (n = 117) or from the STAR file (n = 3), was used. Cox regression analysis was used to test the associations between the independent predictor variables of interest on time until posttransplant skin cancer. Hazard ratios (HR) and 95% CIs were adjusted for all predictors. Binary tests of interaction were performed, and the proportionality of hazards assumption was tested using the Schoenfeld test. To acknowledge clustering effects by transplant center, a shared frailty model with γ-distributed frailties was used in the Cox regression analysis (equivalent to a mixed model where the transplant center is a random effects variable).[30] The skin cancer–specific HR was calculated in the presence of competing risk, defined as death from all causes, using the Fine and Gray proportional subhazard method.[31] Competing risk regression yielded similar HRs as those obtained with Cox regression.

To investigate differences in transplant cohorts (transplant year 2003 vs 2008) and other temporal trends, all analyses were conducted for the overall cohort and stratified by transplant year 2003 vs 2008 (eTables 2-4 in the Supplement).

Several sensitivity analyses were conducted to account for missing data. Data missing more than 10% of observations were the outcomes of SCC (36%), MM (36%), MCC (37%), and predictor of pretransplant skin cancer (39%) (eTable 1 in the Supplement). On logistic regression analysis, thoracic OTRs and patients transplanted in southern latitudes were more likely to be missing outcomes. First, inverse probability weighting (ie, weighting on the inverse of the probability of not missing the outcome) was used to account for missing data.[32] A logistic regression model for missing outcomes was developed, and the analysis was run adjusting for missing data through the weighting scheme. To acknowledge clustering effects by transplant center, the Huber/White method of cluster-robust standard error was applied to the Cox regression analysis.[33] In a second sensitivity analysis, chained equations multiple imputation (MI) was performed.[34] Twenty imputed data sets were created, and all missing outcomes and predictor were included. This strategy was limited by a significant overlap between the patients missing the outcomes and those missing the predictor. To address differential missingness of data between the participating centers, a third sensitivity analysis excluding centers with more than 20% of missing outcome data was performed. The final model was robust to the above sensitivity analyses; any differences in the results are noted in the results section.

Results

Study Population

A total of 10 649 adult subjects received a primary transplant in 2003 (n = 5004) or 2008 (n = 5645), contributing 59 923 person-years of follow-up. The median (interquartile range [IQR]) follow-up was 6 (3-8) years; 10 years in those transplanted in 2003 (IQR, 3-11), and 6 years in those transplanted in 2008 (IQR, 3-7). At the end of follow-up, 6729 (63%) patients were alive, 2773 (26%) were deceased, and 1147 (11%) were lost to follow-up.

Cohort demographics are summarized in **Table 1**, along with the national demographics of OTRs transplanted in 2003 or 2008. Compared to all OTRs who received a primary transplant in the United States in 2003 or 2008, our study group was older, had a higher proportion of white patients, and had undergone thoracic OTRs ($P < .001$).

Skin Cancer Incidence

A total of 861 patients (8%) developed posttransplant skin cancer, yielding an IR of 1437 per 100 000 person-years (**Table 2**). The stratum-specific IR was highest for thoracic transplant recipients (2426 per 100 000 person-years), whites (2039 per 100 000 person-years), patients 50 years or older at transplant (2032 per 100 000 person-years), men (1718 per 100 000 person-years), and those transplanted in 2008 vs 2003 (1651 per 100 000 person-years). Analysis of the renal transplant group specifically demonstrated that the stratum-specific IR for this subgroup was 1280 per 100 000 person-years. The cumulative incidence of skin cancer–free survival was lower for those transplanted in 2008 vs 2003, as shown in the Kaplan-Meier plots in the **Figure** (log rank $P < .001$) (eTable 2 in the Supplement presents the IR of skin cancer stratified by covariates for years of transplant 2003 and 2008). The majority (n = 812 [94%]) of skin cancers were SCC, yielding an IR of 1355 per 100 000 person-years (**Table 3**). The incidence of posttransplant MM (n = 75) was 125 per 100 000 person-years. Only 2 cases of posttransplant MCC were documented.

Predictors of Posttransplant Skin Cancer

Several predictors of skin cancer were identified (**Table 4**). The adjusted HR for overall skin cancer was 4.69 (95% CI, 3.61-6.09) in association with a history of previous pretransplant skin cancer ($P < .001$), 1.61 (95% CI, 1.34-1.89) for male sex ($P < .001$), 1.51 (95% CI, 1.26-1.82) for thoracic organ transplantation ($P < .001$), 7.79 (95% CI, 5.34-11.37) for white race ($P < .001$), 2.65 (95% CI, 2.12-3.21) for patients 50 years or older at transplant ($P < .001$), and 1.59 (95% CI, 1.33-1.91) for being transplanted in 2008 vs 2003 ($P < .001$). Latitude was not statistically associated with skin cancer risk (HR, 1.01 [95% CI, 0.99-1.02] per degree latitude; $P = .97$).

The adjusted HR for SCC and MM were similar to those for overall skin cancer (Table 4), falling short of statistical significance in MM due to the small number of events. A positive history of pretransplant MM had a higher HR (7.15 [95% CI, 3.31-15.46]; $P < .001$) compared with that observed for SCC or overall skin cancer (HR, 4.71 [95% CI, 3.60-6.16] and 4.69 [95% CI, 3.61-6.09], respectively; $P < .001$).

Table 1. Baseline Demographics of the Study Cohort and All US OTR in 2003 and 2008

Characteristic	Study Cohort	All OTR	*P* Value
Total, No.	10 649	44 469	
Age at transplant, y			
Mean (SD)	51 (12)	50 (13)	<.001
Median (IQR)	53 (44-60)	52 (42-60)	
18-29	706 (6)	3347 (7)	<.001
30-39	1175 (11)	5319 (12)	
40-49	2242 (21)	9523 (21)	
50-59	3504 (33)	14 301 (32)	
60-69	2532 (24)	10 061 (23)	
≥70	490 (5)	1918 (4)	
≥50	6526 (61)	26 280 (59)	<.001
<50	4123 (39)	18 189 (41)	
Sex			
Male	6776 (64)	28 116 (63)	.07
Female	3873 (36)	16 353 (37)	
Race			
White	7184 (67)	27 762 (63)	<.001
Black	1503 (14)	8555 (19)	
Hispanic	1239 (11)	5512 (12)	
Asian	561 (5)	1914 (4)	
Other[a]	163 (2)	725 (2)	
White	7184 (67)	27 762 (62)	<.001
Nonwhite	3465 (33)	16 706 (38)	
Organ			
Lung[b]	981 (9)	2415 (5)	<.001
Heart	1017 (10)	3456 (7)	
Kidney	5158 (48)	26 679 (61)	
Pancreas[c]	386 (4)	1905 (5)	
Liver	3107 (29)	10 014 (21)	
Thoracic	1998 (19)	5871 (13)	<.001
Abdominal	8651 (81)	38 598 (86)	
Year transplanted			
2003	5004 (47)	21 512 (47)	.90
2008	5645 (53)	24 471 (53)	
Latitude, °N[d]			
Mean (SD)	39 (7)	NA	
Median (IQR)	40 (34-43)	NA	

Abbreviations: IQR, interquartile range; °N, degrees north; OTR, organ transplant recipients.

[a] Includes American Indian or Alaska Native (n = 79), Native Hawaiian or other Pacific Islander (n = 37), multiracial (n = 46), and unknown (n = 1).

[b] Includes heart-lung (n = 15).

[c] Includes kidney-pancreas (n = 296).

[d] Latitude coordinates were only available for the study cohort. The United States is located on the geographic coordinates of 40 °N latitude and 100 °W longitude in North America.

The HR obtained with inverse probability weighting in the first sensitivity analysis differed only with thoracic organ, and this not significantly. The nonsignificance of this predictor was likely due to collinearity between thoracic organ and transplant center, and this motivated our choice to use shared frailty models in the main analysis. Truncating weights at the 90th, 95th, and 99th centiles yielded similar HRs to inverse probability weighting analysis with no weight truncation.

Discussion

Incidence and Predictors of Skin Cancer in OTRs

This study provides a national patient population estimate for posttransplant skin cancer incidence in the United States. The IR of overall skin cancer was high at 1437 per 100 000 person-years. Most cancers were SCC, which had the highest IR at 1355 per 100 000 person-years. By comparison, the US general adult population age-adjusted IR of SCC is 38 per 100 000.[35] The IR of MM was 125 per 100 000, also elevated compared with the general population rate of 9 to 18 per 100 000.[35,36] We observed 2 cases of MCC, compared with an expectation of 0.079 (based on an expected IR of 0.13 per 100 000 in the general population).[8] This yields the ratio of observed to expected of 25.3 (95% CI, 3.1%-91.3%) Poisson observation to its expectation.[37] To further put these numbers into context, the skin cancer incidence rate in OTRs is nearly 5 times the rate of all cancers combined in the overall US population (448.7 per 100 000).[38]

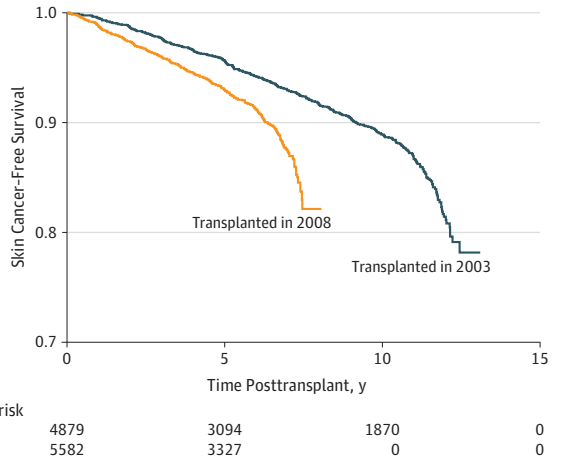
Our results highlight several risk factors for posttransplant skin cancer. The HR of posttransplant skin cancer was elevated in whites, men, thoracic transplant recipients, and patients 50 years or older at transplant. The corresponding IR for these groups underscore the magnitude of these effects: in whites the IR (per 100 000) was 2039, a 22-fold higher rate than

Table 2. Posttransplant Overall Skin Cancer Incidence Rate; Total and Unadjusted Stratum-Specific[a]

Characteristic	Skin Cancer, No.	Incidence Rate (95% CI)
Total	861	1436.83 (1343.99-1536.01)
Sex		
Male	641	1717.95 (1589.98-1856.23)
Female	220	972.93 (852.50-1110.38)
Race		
White	824	2038.66 (1904.11-2182.72)
Nonwhite	37	189.75 (137.48-261.90)
Organ		
Thoracic	261	2425.87 (2148.72-2738.77)
Abdominal	600	1220.81 (1126.93-1322.51)
Age, y		
≥50	702	2031.68 (1886.82-2187.67)
<50	159	626.69 (536.48-732.08)
Year transplanted		
2003	431	1272.38 (1157.76-1398.36)
2008	430	1650.65 (1501.78-1814.28)

[a] Incidence rate is expressed per 100 000 person-years.

Figure. Posttransplant Skin Cancer–Free Survival



Kaplan-Meier plot showing the proportion of organ transplant recipients with skin cancer–free survival 1 to 15 years after their primary transplant, stratified by transplant year (2003 vs 2008). Overall, 10 649 transplants are included; 5004 transplanted in 2003 and 5645 transplanted in 2008 ($P < .001$; log-rank test for difference in skin cancer–free survival between patients transplanted in 2003 vs 2008).

Table 3. Posttransplant Incidence Rate (Overall, SCC, MM, and MCC)

Cancer Type	Total, No.	Incidence Rate (95% CI)[a]
All skin cancers	861	1436.83 (1343.99-1536.01)
SCC	812	1355.05 (1264.98-1451.54)
MM	75	125.15 (99.81-156.94)
MCC	2	3.33 (0.83-13.34)

Abbreviations: MCC, Merkel cell carcinoma; MM, malignant melanoma; SCC, squamous cell carcinoma.

[a] Incidence rate is expressed per 100 000 person-years.

in nonwhites; for men, patients 50 years or older at transplant, and thoracic OTR, the IRs were 1.7-fold to 3-fold higher than for women, patients younger than 50 years at transplant, or abdominal OTRs, respectively.

Effect of Era of Transplantation on Skin Cancer

Patients transplanted in 2008 vs 2003 had a higher IR of skin cancer (1651 vs 1272 per 100 000 person-years) (Table 2) (eTable 2 in the Supplement). We postulated that this might be due to improved documentation of skin cancer history in the more recent era (2008), but the difference persisted when the follow-up time was limited to 2009 and beyond (eTable 3 in the Supplement). We also postulated that the difference might be due to improved overall survival in the more recent era due to newer immunosuppressive agents, but the increase reflects adjustment for death as a competing risk. We postulate that the difference may be due to more aggressive immediate posttransplant immunosuppression in the more recent era. The risk model stratified by transplant year was not different to that of the overall cohort, so this temporal trend is not working through any of the risk factors (eTable 4 in the Supplement).

Effect of Pretransplant UV Exposure on Skin Cancer

We used latitude of residence as proxy for prior UV exposure and hypothesized that subjects living in southern latitudes have a higher incidence of posttransplant skin cancer.[28,29,39] The HRs for other factors remained unchanged when latitude was removed from the model, and HRs remained unchanged in a model restricting to the US mainland latitude coordinates. There are several possible explanations for the absence of an effect of latitude on skin cancer. Although latitude is used as proxy for prior UV exposure in the general population,[40-42] it may not be a good measure of pretransplant UV exposure in OTRs. Also, latitude coordinates were obtained by geocoding the patient's zip code at transplant, which may not represent the cumulative prior sun exposure[43,44]; survey data on previous sunburn may be a better proxy for prior UV exposure. Lastly, although UV radiation is an established skin carcinogen in the general population,[44-46] the causality may not hold true in OTRs. Research using latitude, AVerage daily total GLObal solar radiation (AVGLO) exposure, and patient-based reports of prior sun exposure history points to a role for UV radiation in skin cancer incidence, but more reliable biomarkers of UV radiation may be needed to substantiate this hypothesis.

Predictors of SCC and MM

The magnitude and significance of the predictors in the model for overall skin cancer was driven by SCC. The model for MM had similar point estimates for the predictors, with wider CIs reflecting a smaller number of observed cases. The effect of pretransplant MM on posttransplant MM risk was larger than that observed for SCC (HR, 7.15; $P < .001$ vs HR, 4.71; $P < .001$). Arron et al[47] observed a similar effect size in a cohort of 185 039 OTRs in the United States where the HR for incident MM in patients with pretransplant MM was 5.4 ($P < .001$).[47]

Limitations

The main limitation of this study was the imperfect capture of outcome data. The primary reason for missing skin cancer data

Table 4. Predictors of Skin Cancer, SCC, and MM

Predictor	Hazard Ratio (95% CI)[a] Skin Cancer	*P* Value	SCC	*P* Value	MM	*P* Value
Pretransplant skin cancer						
No	1 [Reference]		1 [Reference]		1 [Reference]	
Yes	4.69 (3.61-6.09)	<.001	4.71 (3.60-6.16)[b]	<.001	7.15 (3.31-15.46)[c]	<.001
Female	1 [Reference]		1 [Reference]		1 [Reference]	
Male	1.61 (1.34-1.89)	<.001	1.67 (1.41-2.01)	<.001	1.26 (0.73-2.20)	.41
Organ transplant						
Abdominal	1 [Reference]		1 [Reference]		1 [Reference]	
Thoracic	1.51 (1.26-1.82)	<.001	1.53 (1.265-1.85)	<.001	1.33 (0.72-2.47)	.35
Race						
Nonwhite	1 [Reference]		1 [Reference]		1 [Reference]	
White	7.79 (5.34-11.37)	<.001	8.18 (5.49-12.18)	<.001	7.21 (2.33-23.31)	.01
Age, y						
<50	1 [Reference]		1 [Reference]		1 [Reference]	
≥50	2.65 (2.12-3.21)	<.001	2.73 (2.24-3.34)	<.001	1.95 (1.05-3.61)	.03
Year transplanted						
2003	1 [Reference]		1 [Reference]		1 [Reference]	
2008	1.59 (1.33-1.91)	<.001	1.61 (1.34-1.93)	<.001	1.65 (0.89-3.06)	.11
Latitude	1 [Reference]		1 [Reference]		1 [Reference]	
Latitude, 1 °N increase	1.01 (0.99-1.02)	.97	1.01 (0.99-1.02)	.94	0.98 (0.96-1.01)	.54

Abbreviations: MM, malignant melanoma; SCC, squamous cell carcinoma.

[a] Hazard ratios are adjusted for other covariates.

[b] History of pretransplant SCC.

[c] History of pretransplant MM.

was the failure to have a dermatologic history noted in the medical record. This may occur if patients were followed by dermatologists in the community and did not report their skin cancers to the transplant team. This limitation was addressed by comparing the results of several sensitivity analyses using methods to address missing data as previously noted. To account for variance between the 26 participating transplant centers, we incorporated a shared frailty model into the Cox regression to account for random effects due to transplant center.

As medical record documentation is the gold standard for skin cancer malignancy reporting, this study highlights the need for better documentation of skin cancer history. Posttransplant skin cancer can be reported to OPTN via malignancy reporting forms, but dermatologists may not be aware that the transplant team is able to register these tumors with OPTN. Future analysis of this data set will investigate the validity of OPTN posttransplant malignancy reporting for skin cancer.

Further, the sample was biased toward patients seen in academic transplant centers with a dermatology department. When comparing the TSCN cohort with all US patients transplanted in 2003 and 2008, there was a small but statistically significant increase in the proportion of subjects who were older, white, and a recipient of a thoracic transplant. Because these are known risk factors for posttransplant skin cancer, it is possible that our IR estimate is in the upper bounds of the true population value. Balanced against the potential for under-capture of skin cancer outcomes, we anticipate that these data achieve reasonable accuracy.

Prior research has demonstrated that specific immunosuppressive agents such as azathioprine confer increased risk for skin cancer in OTRs. Data on the duration and dosage of medication exposure required to inform this type of pharmacologic study was not available to this cohort since it is not included in the OTPN database. The utility of the data presented is to inform risk prediction at the time of transplant, before posttransplant drug exposures. Future research is needed to determine whether skin cancer risk can be mitigated through optimization of immunosuppressive regimes.

Conclusions

The high incidence of posttransplant skin cancer highlights the need for tumor surveillance after organ transplantation, especially in patients with high-risk features. These data can be used to inform risk stratification and screening guidelines for skin cancer in OTRs. To our knowledge, Germany executed the first nationwide skin cancer screening program for the general population in 2008; its effectiveness in reducing the mortality and morbidity of skin cancer is under evaluation.[45,46,48] A follow-up goal of this study is to develop a prediction tool for posttransplant skin cancer.

ARTICLE INFORMATION

Correction: This article was corrected on February 1, 2017, for an incorrect author affiliation and an error in the abstract Results paragraph and the Findings paragraph of the Key Points.

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NOTABLE NOTES

Early Reports of "Sycosis"

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Sycosis is a medical term that creates confusion in the ancient texts. The term is used for both the description of a skin disease and for trachoma. This Notable Note aims at shedding light on the skin disease defined as sycosis, after the Greek term for "fig" (σύκο)—since its appearance resembles the inner part of the fruit—and presenting the descriptions of ancient authors.

According to Galen (AD 2nd century), Archigenes (AD 1st century) defined sycosis as exanthemata of the beard, also called mentagra (μανταγρες), or wild lichen, while Heraclides of Tarentum (2nd century BC) described sycosis of the head and beard as having the form of protruding ulcers.[1] Galen himself described sycosis as small, hard ulcers appearing on the beard that are composed partly of thick and partly of thin serous humor and ulcerating rapidly if not treated with highly drying medicaments.[1] Celsus (AD 1st century) described sycosis as an ulceration of 2 types, both appearing in areas covered by hair: (1) indurated and circular ulceration and (2) moist ulceration with an irregular outline. In the first type, which appears mostly on the beard, there is a scanty and glutinous discharge, while in the second type, which appears mainly on the scalp, the discharge is abundant and malodorous.[2] Pliny the Elder (AD 1st century) wrote of an affliction called *mentagra* in Latin, or *lichen* in Greek, that affected mainly the upper-class citizens and was dispersed through kissing. Aetius of Amida (AD 5-6th century), Paulus Aegineta (AD 7th century), and Paulus Nicaaensis (circa AD 7th-10th centuries) described as sycosis either infections of the eyelids or "ulcerous excrescences which are round, somewhat hard, red, and accompanied with pain" arising mostly on the head but also on other parts of the body.[3]

From a modern point of view, sycosis is defined as an edematous growth in form of a fig, usually concerning folliculitis involving the cutaneous areas covered by beard hair. Anatomically, it is characterized by formation of pustular nodules or even intradermal abscesses. There are 2 different anatomoclinical forms of sycosis: staphylococcal sycosis and fungal sycosis. The "indurated and circular ulceration" described by Celsus may correlate with Tinea barbae, the most common responsible agent for fungal sycosis. As far as Celsus's description of sycosis as "moist, with irregular outline ulceration" is concerned, he may have been referring to Celsus kerion of the scalp hair or less possibly staphylococcal infection in Quinquaud folliculitis decalvans (neutrophilic cicatricial alopecia), found in patients with a deficient host immune response. Finally, the descriptions of Paulus Aegineta, Aetius, and Paulus Nicaaensis possibly referred to the whitish follicles of the inner eyelid appearing in trachoma, a contagious affection caused by *Chlamydia trachomatis*.

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