Risk Factors for Keratinocyte Carcinoma in Recipients of Allogeneic Hematopoietic Cell Transplants

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IMPORTANCE Allogeneic hematopoietic cell transplant (alloHCT) is known to increase the risk for keratinocyte carcinoma. The extent to which host characteristics, including pigmentary phenotype and UV radiation exposure, contribute is unknown.

OBJECTIVE To identify and validate independent risk factors for keratinocyte carcinoma after alloHCT, including those associated with the transplant and the host.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study analyzed a consecutive sample of alloHCT recipients from January 1, 2000, to December 31, 2014, at the Mayo Clinic, Rochester, Minnesota (n = 872) and University Hospitals Cleveland Medical Center, Cleveland, Ohio (n = 147). Participants from the Mayo Clinic were randomly allocated (2:1) into discovery (n = 581) and validation (n = 291) cohorts. Time to first keratinocyte carcinoma and information about transplant- and host-associated risk factors were extracted. A multivariate keratinocyte carcinoma risk model was created using a stepwise Cox proportional hazards regression model with $P < .05$ for entry that incorporated all covariates that were individually statistically significant at $\alpha = 0.05$ in the discovery cohort. The risk model was first internally validated using the Mayo Clinic validation cohort and then externally validated using the independent cohort of alloHCT recipients at University Hospitals Cleveland Medical Center. Data were analyzed from March 13, 2018, to June 12, 2019.

EXPOSURES Allogeneic hematopoietic cell transplant.

MAIN OUTCOMES AND MEASURES The primary outcome was time to development of the first cutaneous keratinocyte carcinoma after alloHCT; secondary outcome, time to development of the first individual basal and/or squamous cell carcinoma after alloHCT.

RESULTS Of the 872 alloHCT recipients identified in the Mayo Clinic cohort (520 men [59.6%]; mean [SD] age, 48.3 [12.6] years), 95 (10.9%) developed keratinocyte carcinoma after alloHCT during 5349 person-years of follow-up. Of the 147 alloHCT recipients in the external validation cohort (86 men [58.5%]; mean [SD] age, 47.9 [17.5] years), 18 (12.2%) developed keratinocyte carcinoma after alloHCT in 880 person-years of follow up. Risk factors independently associated with keratinocyte carcinoma after alloHCT included age (hazard ratio [HR] per 10 years, 1.72; 95% CI, 1.21-2.42), chronic lymphocytic leukemia (HR, 2.47; 95% CI, 1.20-5.09), clinically photodamaged skin (HR, 3.47; 95% CI, 1.87-6.41), and history of cutaneous squamous cell carcinoma (HR, 2.60; 95% CI, 1.41-5.91). Harrell concordance statistics were 0.81 (95% CI, 0.72-0.90) and 0.86 (95% CI, 0.74-0.98) for internal and external validation of the keratinocyte carcinoma risk model, respectively.

CONCLUSIONS AND RELEVANCE This study found validated independent risk factors for keratinocyte carcinoma after alloHCT that are enriched with host- compared with transplant-associated risk factors. These findings highlight the importance of assessing host-associated risk factors for keratinocyte carcinoma in patients eligible for alloHCT. Future studies should examine whether keratinocyte carcinoma risk stratification before alloHCT may inform long-term surveillance strategies.
Recipients of allogeneic hematopoietic cell transplant (alloHCT) are at increased risk for developing secondary malignant neoplasms, including skin cancer. Moreover, skin cancers are an important public health concern in long-term survivors of alloHCT because these cancers may present aggressively and lead to significant morbidity.\textsuperscript{2,3} Transplant-associated risk factors for keratinocyte carcinoma, including basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (SCC), after alloHCT are well described and include chronic lymphocytic leukemia, myeloablative total body irradiation (TBI), and chronic graft-vs-host disease (GVHD), among others.\textsuperscript{2-9} However, host-associated risk factors, including pigmentary phenotype and history of UV radiation exposure, are responsible for most primary skin cancer risk in the general population and have not been well studied in alloHCT recipients.\textsuperscript{10,11}

Host-associated risk factors for skin cancer development in alloHCT recipients are incompletely described in part because studies using long-term retrospective cohorts are generally unable to capture these risk factors in sufficient detail owing to incomplete or unknown follow-up with dermatology.\textsuperscript{2,4-7,9} For example, although white race and non-Hispanic white ethnicity are associated with an increased risk of keratinocyte carcinoma after alloHCT, the association between skin cancer risk and precise characterizations of pigmentary phenotype and sun sensitivity, such as Fitzpatrick skin type, are lacking.\textsuperscript{12,13} Similarly, the extent to which prior UV radiation exposure is associated with secondary skin cancer risk in alloHCT recipients remains unknown.

As the number of long-term survivors of alloHCT grows, it is becoming increasingly important to accurately identify alloHCT recipients at highest risk for developing secondary malignant neoplasms after transplant.\textsuperscript{14} Therefore, we first aimed to identify independent risk factors for keratinocyte carcinoma after alloHCT, including those associated with transplant and host. Second, we aimed to validate risk factors in a multicenter fashion.

**Methods**

**Participants and Outcomes**

This retrospective cohort study was approved by the institutional review boards at the Mayo Clinic, Rochester, Minnesota, and University Hospitals Cleveland Medical Center (UHCMC), Cleveland, Ohio. The institutional review boards of both institutions waived the need for informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. Patients older than 18 years who underwent alloHCT from January 1, 2000, to December 31, 2014, and who survived for at least 30 days were identified from alloHCT databases and electronic medical records at each institution. Patient demographics, year of transplant, skin cancers (SCC or BCC) developing after alloHCT, skin cancer risk factors, follow-up time, and vital status at follow-up were extracted from the medical records using a standardized data collection tool.

The primary outcome was time to development of the first keratinocyte carcinoma (cutaneous SCC or BCC) after alloHCT. Secondary outcomes included time to development of the first individual SCC or BCC after alloHCT. Patients developing multiple skin cancers of the same type were treated as a single participant, with the first skin cancer classified as the time to event. Skin cancers developing at an unknown time after alloHCT were excluded. Five-year cumulative incidences for SCC and BCC were calculated as percentages with 95% CIs.

**Risk Factors**

Risk factors for SCC and BCC in alloHCT recipients, or in the general population for select risk factors, were identified a priori from a literature review (eTable 1 in the Supplement). Risk factors were categorized as transplant and host associated. Transplant-associated risk factors defined as related to alloHCT included type of primary disease (myeloid disorders, lymphoid leukemia, lymphoproliferative disorders, plasma cell disorders, nonneoplastic disorders, or other leukemia not otherwise specified), conditioning regimen (myeloablative, reduced intensity [RI], or nonmyeloablative [NMA]), TBI, and cumulative duration of voriconazole exposure. Additional transplant-associated risk factors included those related to immunosuppressive regimens, specifically exposure to methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and azathioprine; cumulative duration of immunosuppression; and those related to GVHD, specifically the presence of acute GVHD, chronic GVHD of any site, chronic GVHD with skin involvement, cumulative duration of chronic GVHD, and maximum severity of chronic GVHD (none, mild, moderate, or severe).

Host-associated risk factors were defined as those related to the patient and included age at alloHCT, sex, and family history of skin cancer; related to pigmentary phenotype, specifically Fitzpatrick skin type and dysplastic nevi documented clinically before alloHCT; related to radiation exposure before alloHCT, specifically phototherapy, radiotherapy, outdoor occupation, and clinically photodamaged skin documented before alloHCT; and related to prior skin cancers, specifically a history of SCC, BCC, or melanoma before alloHCT.

**Key Points**

**Question** To what extent do host characteristics contribute to skin cancer risk after allogeneic hematopoietic cell transplant (alloHCT)?

**Findings** In this cohort study of 1019 patients undergoing alloHCT, validated independent risk factors for keratinocyte carcinoma in recipients of alloHCT included a predominance of host-associated rather than transplant-associated factors, such as age, chronic UV radiation exposure manifested as clinically photodamaged skin and history of cutaneous squamous cell carcinoma, and chronic lymphocytic leukemia.

**Meaning** Host-associated risk factors for keratinocyte carcinoma, including pigmentary phenotype and UV radiation exposure, should be assessed in patients eligible for alloHCT.
Photodamaged skin before alloHCT was determined based on specific documentation in the physical examination, including dermatoheliosis, Glogau scale, actinic damage, or photodamage. Fitzpatrick skin type is a numerical classification used for measuring human skin pigmentation and sun sensitivity, with types I and II corresponding to pigmented phenotypes with a greater risk for burning and less tanning after UV radiation exposure compared with types III to VI.15

Risk Factor Identification and Validation
The Mayo Clinic cohort was chosen to identify independent risk factors for keratinocyte carcinoma given its larger size and close follow-up with hematology and dermatology at the same institution. This cohort was randomly divided in a 2:1 ratio into discovery and validation cohorts. Differences in demographic and clinical variables between the discovery and validation cohorts were assessed using unpaired 2-tailed t tests for continuous variables and χ² tests for categorical variables.

Statistical Analysis
Data were analyzed from March 13, 2018, to June 12, 2019. Within the discovery cohort, univariate Cox proportional hazards regression models were used to calculate hazard ratios (HRs) with 95% CIs to determine the statistical significance of the difference in the distribution of individual risk factors between patients with and without the primary and secondary outcomes. Cumulative duration of immunosuppression and voriconazole exposure were considered as time-dependent covariates. All risk factors were assessed for correlation before model generation. Multivariate models were externally validated in an independent UHCMC cohort, and receiver operating characteristic curves were similarly generated at 24, 48, 72, and 96 months, yielding Harrell C statistics. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc).

Results
The Mayo Clinic cohort consisted of 872 alloHCT recipients (520 men [59.6%] and 352 women [40.4%]; mean [SD] age, 48.3 [12.6] years) from January 1, 2000, to December 31, 2014 (Table 1). In total, 95 alloHCT recipients (10.9%) developed keratinocyte carcinoma after alloHCT in 5349 person-years of follow-up (eFigure A-C in the Supplement). Specifically, 62 patients developed 290 SCCs (range, 1-28) and 53 patients developed 175 BCCs (range, 1-27). Of the 95 patients developing any keratinocyte carcinoma, 37 (39.0%) developed a single SCC or BCC after alloHCT, and 23 (24.2%) developed both SCC and BCC (Table 2). After random allocation, the Mayo Clinic discovery (n = 581) and validation (n = 291) cohorts did not differ by age at alloHCT (mean [SD] age, 48.5 [12.6] vs 47.8 [12.6] years), sex (male, 355 [61.1%] vs 165 [56.7%]), year of transplant (eg, 2010-2014, 299 [51.5% vs 147 [50.5%]), follow-up time (mean [SD], 41.8 [41.6] vs 42.8 [44.5] months), vital status at follow-up (alive, 230 [39.6%] vs 119 [40.9%]), or 5-year cumulative incidence of skin cancer (SCC, 12.3% [95% CI, 8.5%-16.3%] vs 9.8% [95% CI, 4.8%-14.8%]; BCC, 9.1% [95% CI, 5.4%-12.8%] vs 5.8% [95% CI, 2.0%-9.6%]) (P > .05 for all).

The number and percentage of alloHCT recipients in the Mayo Clinic discovery cohort with each transplant- and host-associated risk factor who did and did not develop keratinocyte carcinoma, SCC, or BCC after alloHCT are provided in eTable 2 in the Supplement. In univariate analyses of the Mayo Clinic discovery cohort (Table 3), transplant-associated risk factors for keratinocyte carcinoma after alloHCT included chronic lymphocytic leukemia (HR, 3.35; 95% CI, 2.00-5.62), R1/NMA conditioning regimens (HR vs myeloablative regimens, 2.52; 95% CI, 1.52-4.17), cumulative duration of immunosuppression (HR per 100 days, 1.03; 95% CI, 1.01-1.05), chronic GVHD at any site (HR, 1.96; 95% CI, 1.04-3.68), chronic GVHD involving the skin (HR, 2.79; 95% CI, 1.58-4.90), and higher maximum severity of chronic GVHD (HR for moderate/severe vs none/mild, 2.16; 95% CI, 1.25-3.71). Chronic GVHD (HR, 27.74, 95% CI, 4.79-159.89) and cumulative duration of immunosuppression (HR per 100 days, 1.05; 95% CI, 1.02-1.08) were both significantly associated with an increased risk of SCC after alloHCT. Exposures to cyclosporine (HR, 5.88; 95% CI, 2.08-16.67) and tacrolimus (HR, 0.17; 95% CI, 0.06-0.48) were significantly associated with an increased and decreased risk, respectively, of BCC after alloHCT.

In univariate analyses of the Mayo Clinic discovery cohort (Table 4), host-associated risk factors for keratinocyte carcinoma after alloHCT included age at alloHCT (HR per 10 years, 1.97; 95% CI, 1.48-2.59), male sex (HR, 1.96; 95% CI, 1.12-3.45), pigmented phenotype associated with increased sun sensitivity (HR for Fitzpatrick skin type II vs III-VI, 3.57; 95% CI, 1.22-10.39), outdoor occupation (HR, 1.89; 95% CI, 1.02-3.51), and clinically photodamaged skin documented before alloHCT (HR, 5.08; 95% CI, 3.10-8.33). A history of SCC before alloHCT (HR, 7.81; 95% CI, 3.94-15.60) or BCC (HR, 2.90; 95% CI, 1.04-8.00) was also significantly associated with keratinocyte carcinoma after alloHCT. Patients with Fitzpatrick skin type I or II developed 49 (92.5%) of all keratinocyte carcino-
mas. Pigmentary phenotype was more strongly associated with SCC than BCC (HR for Fitzpatrick skin type I vs III-VI, 9.62 [95% CI, 1.34-71.43]; HR for Fitzpatrick skin type II vs III-VI, 6.17 [95% CI, 1.23-31.26]), whereas age at alloHCT (HR per 10 years, 1.57; 95% CI, 1.11-2.22) and phototherapy exposure before alloHCT (HR per 10 years, 3.65; 95% CI, 1.44-9.18) were more strongly associated with BCC than SCC.

In multivariate analyses of the Mayo Clinic discovery cohort using stepwise Cox proportional hazards regression modeling (Table 5), risk factors independently associated with keratinocyte carcinoma after alloHCT included age at alloHCT (HR per 10 years, 1.72; 95% CI, 1.21-2.42), chronic lymphocytic leukemia (HR, 2.47; 95% CI, 1.20-5.09), clinically photodamaged skin documented before alloHCT (HR, 3.47; 95% CI, 1.87-6.41), and history of SCC before alloHCT (HR, 2.60; 95% CI, 1.41-5.91). The final keratinocyte carcinoma risk model did not change using forward or backward selection or P ≤ .10 for final inclusion. Strong associations were also present in the multivariate risk model for SCC, with chronic GVHD (HR, 3.08; 95% CI, 4.23-228.00) and pigmentary phenotype (HR for Fitzpatrick skin type I vs III-VI, 20.30 [95% CI, 2.43-166.67]) each independently conferring significantly increased risk. The multivariate risk model for BCC included age at alloHCT (HR per 10 years, 1.21; 95% CI, 1.12-2.40) and phototherapy exposure before alloHCT (HR, 3.81; 95% CI, 1.48-9.82).

An independent cohort of 147 alloHCT recipients at UHCMC was chosen as the external validation cohort (eTable 3 in the Supplement). Eighteen patients (12.2%) developed at least 1 keratinocyte carcinoma (7 SCC and 15 BCC) after alloHCT in 880 person-years of follow-up. The UHCMC cohort did not differ from the Mayo Clinic cohort with regard to the age at alloHCT (mean [SD], 48.3 [12.6] vs 47.9 [17.5] years), sex (male, 520 [59.6%] vs 86 [58.5%]), follow-up time (mean [SD], 41.8 [41.7] vs 48.6 [45.7] months), or type of skin cancers after alloHCT (62 SCC [7.1%] and 53 BCC [6.1%] vs 7 SCC [4.8%] and 15 BCC 10.2%]) (P > .05 for all).

### Table 1. Characteristics of the Mayo Clinic Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 872)</th>
<th>Discovery cohort (n = 581)</th>
<th>Validation cohort (n = 291)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at alloHCT, mean (SD), y</td>
<td>48.3 (12.6)</td>
<td>48.5 (12.6)</td>
<td>47.8 (12.6)</td>
<td>.44</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>520 (59.6)</td>
<td>355 (61.1)</td>
<td>165 (56.7)</td>
<td>.21</td>
</tr>
<tr>
<td>Female</td>
<td>352 (40.4)</td>
<td>226 (38.9)</td>
<td>126 (43.3)</td>
<td></td>
</tr>
<tr>
<td>Year of transplant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000-2004</td>
<td>162 (18.6)</td>
<td>107 (18.4)</td>
<td>55 (18.9)</td>
<td>.97</td>
</tr>
<tr>
<td>2005-2009</td>
<td>264 (30.3)</td>
<td>175 (30.1)</td>
<td>89 (30.6)</td>
<td></td>
</tr>
<tr>
<td>2010-2014</td>
<td>446 (51.1)</td>
<td>299 (51.5)</td>
<td>147 (50.5)</td>
<td></td>
</tr>
<tr>
<td>Follow-up, mean (SD), mo b</td>
<td>41.8 (41.7)</td>
<td>41.8 (41.6)</td>
<td>42.8 (44.5)</td>
<td>.74</td>
</tr>
<tr>
<td>Vital status at end of follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>349 (40.0)</td>
<td>230 (39.6)</td>
<td>119 (40.9)</td>
<td>.77</td>
</tr>
<tr>
<td>Dead</td>
<td>519 (59.5)</td>
<td>347 (59.7)</td>
<td>172 (59.1)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (0.5)</td>
<td>4 (0.7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Skin cancer after alloHCT c</td>
<td></td>
<td></td>
<td></td>
<td>.23</td>
</tr>
<tr>
<td>SCC</td>
<td>62 (7.1)</td>
<td>44 (7.6)</td>
<td>18 (6.2)</td>
<td></td>
</tr>
<tr>
<td>BCC</td>
<td>53 (6.1)</td>
<td>39 (6.7)</td>
<td>14 (4.8)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>777 (89.1)</td>
<td>511 (88.0)</td>
<td>266 (91.4)</td>
<td></td>
</tr>
<tr>
<td>5-y Cumulative incidence, % (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCC</td>
<td>11.5 (8.3-14.6)</td>
<td>12.3 (8.5-16.3)</td>
<td>9.8 (4.8-14.8)</td>
<td>NA</td>
</tr>
<tr>
<td>BCC</td>
<td>8.0 (5.2-10.8)</td>
<td>9.1 (5.4-12.8)</td>
<td>5.8 (2.0-9.6)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: alloHCT, allogeneic hematopoietic cell transplant; BCC, basal cell carcinoma; NA, not applicable; SCC, squamous cell carcinoma.

* Calculated as difference between discovery vs validation cohort.

b Indicates nonnormal distribution, censored at zero.

c Percentages do not equal 100 because some patients were diagnosed with more than 1 type of skin cancer during follow-up.

### Table 2. Number of Keratinocyte Carcinomas Diagnosed per alloHCT Recipient in the Total Mayo Clinic Cohort

<table>
<thead>
<tr>
<th>No. of BCC</th>
<th>No. of SCC</th>
<th>Patients, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>777</td>
<td>15</td>
</tr>
<tr>
<td>1</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>≥4</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Total No. of patients</td>
<td>810</td>
<td>26</td>
</tr>
</tbody>
</table>

Abbreviations: alloHCT, allogeneic hematopoietic cell transplantation; BCC, basal cell carcinoma; SCC, squamous cell carcinoma.
Table 3. Univariate Cox Proportional Hazards Regression Model Summaries of Transplant-Associated Risk Factors for Keratinocyte Carcinoma, SCC, and BCC After alloHCT in the Mayo Clinic Discovery Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Keratinocyte carcinoma*</th>
<th>SCC</th>
<th>BCC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>AltoHCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloid disorders (vs others)b</td>
<td>1.67 (0.98-2.86)</td>
<td>.06</td>
<td>1.20 (0.61-2.37)</td>
</tr>
<tr>
<td>Lymphoid leukemia (vs others)c</td>
<td>0.35 (0.13-1.00)</td>
<td>.05</td>
<td>0.65 (0.15-2.70)</td>
</tr>
<tr>
<td>Lymphoproliferative (vs others)d</td>
<td>1.77 (0.99-3.15)</td>
<td>.05</td>
<td>1.27 (0.60-2.66)</td>
</tr>
<tr>
<td>CLL (vs others)</td>
<td>3.35 (2.00-5.62)</td>
<td>&lt;.001*</td>
<td>1.38 (0.74-2.56)</td>
</tr>
<tr>
<td>Matched related donor (vs unrelated)</td>
<td>1.04 (0.64-1.67)</td>
<td>.89</td>
<td>0.98 (0.53-1.79)</td>
</tr>
<tr>
<td>HLA mismatches (1 vs 0)</td>
<td>0.47 (0.19-1.19)</td>
<td>.11</td>
<td>0.97 (0.29-3.24)</td>
</tr>
<tr>
<td>RI/NMA conditioning regimen</td>
<td>2.52 (1.52-4.17)</td>
<td>&lt;.001*</td>
<td>1.34 (0.65-2.37)</td>
</tr>
<tr>
<td>TBI exposure</td>
<td>0.66 (0.40-1.08)</td>
<td>.1</td>
<td>0.71 (0.39-1.32)</td>
</tr>
<tr>
<td>Duration of voriconazole treatmentf</td>
<td>1.05 (1.00-1.11)</td>
<td>.07</td>
<td>0.96 (0.89-1.03)</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>0.74 (0.43-1.27)</td>
<td>.27</td>
<td>2.33 (0.91-5.88)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>1.17 (0.70-2.00)</td>
<td>.54</td>
<td>0.61 (0.28-1.32)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>0.83 (0.50-1.41)</td>
<td>.51</td>
<td>1.65 (0.76-3.59)</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>1.89 (1.01-3.54)</td>
<td>.05*</td>
<td>2.33 (0.91-5.97)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>0.65 (0.09-6.93)</td>
<td>.67</td>
<td>NC</td>
</tr>
<tr>
<td>Durationf</td>
<td>1.03 (1.01-1.05)</td>
<td>.003*</td>
<td>1.05 (1.02-1.08)</td>
</tr>
<tr>
<td>GVHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>0.85 (0.52-1.37)</td>
<td>.5</td>
<td>1.22 (0.66-2.27)</td>
</tr>
<tr>
<td>Chronic</td>
<td>1.96 (1.04-3.68)</td>
<td>.04*</td>
<td>27.74 (4.79-159.89)</td>
</tr>
<tr>
<td>Involving skin</td>
<td>2.79 (1.58-4.90)</td>
<td>&lt;.001*</td>
<td>27.74 (4.79-159.89)</td>
</tr>
<tr>
<td>Maximum severity</td>
<td>2.16 (1.25-3.71)</td>
<td>.006*</td>
<td>1.25 (0.56-2.77)</td>
</tr>
<tr>
<td>Durationg</td>
<td>1.04 (0.97-1.08)</td>
<td>.23</td>
<td>1.33 (1.06-1.64)</td>
</tr>
</tbody>
</table>

Abbreviations: alloHCT, allogeneic hematopoietic cell transplant; BCC, basal cell carcinoma; CLL, chronic lymphocytic leukemia; GVHD, graft-vs-host disease; HLA, human leukocyte antigen; HR, hazard ratio; NC, not calculated; NMA, nonmyeloablative; RI, reduced-intensity; SCC, squamous cell carcinoma; TBI, total body irradiation.

a Includes SCC and BCC.
b Includes acute myeloid leukemia, chronic myeloid leukemia, myelofibrosis.
c Includes CLL and other lymphomas.
d Designates covariates included in the multivariate risk modeling.

e Cumulative duration per 100 days.
f Cumulative duration per 10 months.

The multivariate risk model for keratinocyte carcinoma was first validated using the Mayo Clinic (internal) validation cohort, yielding a C statistic of 0.81 (95% CI, 0.72-0.90). Next, the keratinocyte carcinoma multivariate risk model was externally validated using the independent UHCMC cohort, yielding a C statistic of 0.86 (95% CI, 0.74-0.98). The multivariate risk models for the secondary outcomes (SCC and BCC) were also internally and externally validated, yielding C statistics of 0.71 (95% CI, 0.61-0.81) and 0.83 (95% CI, 0.73-0.93), respectively, for SCC and 0.57 (95% CI, 0.50-0.65) and 0.61 (95% CI, 0.50-0.73), respectively, for BCC.

Discussion

This retrospective analysis of contemporary alloHCT recipients identifies a predominance of host-associated risk factors compared with transplant-associated risk factors independently associated with keratinocyte carcinoma after alloHCT. The generalizability of these risk factors is strengthened through strong multicenter validation, with C statistics comparable to a risk factor prognostic model for skin cancer in recipients of solid organ transplant, including white race, male sex, age, and pretransplant skin cancer.17 Notably, well-described transplant-associated risk factors were not independently associated with keratinocyte carcinoma in the final multivariate risk model when a comprehensive set of host-associated risk factors were also considered as covariates. These findings highlight the importance of assessing host-associated keratinocyte carcinoma risk factors in patients eligible for alloHCT, risk stratifying patients before transplant, educating on sun-protective behaviors, and triaging skin cancer surveillance accordingly.

Pigmentary phenotype and history of UV radiation exposure are the primary host-associated risk factors for keratinocyte carcinoma in the general population and are found in 2 recent risk prediction models for SCC in the general population.10,11,18,19 Although white race and non-Hispanic

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white ethnicity are associated with keratinocyte carcinoma after alloHCT in some studies. Self-reported race and ethnicity are poor predictors of sun sensitivity. Fitzpatrick skin types represent more accurate measures of sun sensitivity and pigmentedary phenotype and are independently associated with SCC after solid organ transplant. Similarly, we report Fitzpatrick skin types I and II, corresponding to lighter pigmentedary phenotypes with increased sun sensitivity, as independent risk factors for SCC after alloHCT.

Similar to solid organ transplant, we also report chronic UV radiation exposure before alloHCT, assessed by clinically photodamaged skin and a history of cutaneous SCC, as an independent risk factor for keratinocyte carcinoma after alloHCT. Chronic UV radiation exposure results in photodamaged skin and the development of precancerous actinic keratoses. Photodamaged skin and actinic keratoses are considered part of a disease spectrum, with photodamaged skin surrounding actinic keratoses demonstrating an increased risk for developing keratinocyte carcinoma. Moreover, the risk of immunocompetent adults developing subsequent skin cancers given a history of skin cancer approaches 50% after 5 years, and this risk increases in patients with severely photodamaged skin, increased sun sensitivity, and more than 1 prior skin cancer.

### Table 4. Multivariate Stepwise Cox Proportional Hazards Regression Model Summaries for Keratinocyte Carcinoma, SCC, and BCC After alloHCT in the Mayo Clinic Discovery Cohort

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Keratinocyte carcinoma</th>
<th>SCC</th>
<th>BCC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at alloHCT per 10 y</td>
<td>1.97 (1.48-2.59)</td>
<td>&lt;.001</td>
<td>1.14 (0.78-1.66)</td>
</tr>
<tr>
<td>Male vs female sex</td>
<td>1.96 (1.12-3.45)</td>
<td>.02</td>
<td>1.04 (0.43-2.52)</td>
</tr>
<tr>
<td>Pigmentary phenotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitzpatrick skin type I vs III-V</td>
<td>2.62 (0.63-10.78)</td>
<td>.32</td>
<td>9.62 (1.34-71.43)</td>
</tr>
<tr>
<td>Fitzpatrick skin type II vs III-V</td>
<td>3.57 (1.22-10.39)</td>
<td>.02</td>
<td>6.17 (1.23-31.26)</td>
</tr>
<tr>
<td>Dysplastic nevi</td>
<td>1.81 (0.92-3.54)</td>
<td>.09</td>
<td>1.49 (0.58-3.85)</td>
</tr>
<tr>
<td>Pre-allocHCT radiation exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phototherapy</td>
<td>1.29 (0.70-2.39)</td>
<td>.41</td>
<td>2.04 (0.94-4.45)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>0.77 (0.46-1.26)</td>
<td>.30</td>
<td>0.75 (0.41-1.39)</td>
</tr>
<tr>
<td>Outdoor occupation</td>
<td>1.89 (1.02-3.51)</td>
<td>.04</td>
<td>1.30 (0.61-2.78)</td>
</tr>
<tr>
<td>Photodamaged skin</td>
<td>5.08 (3.10-8.33)</td>
<td>&lt;.001</td>
<td>1.35 (0.73-2.49)</td>
</tr>
<tr>
<td>Pre-allocHCT skin cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCC</td>
<td>2.90 (1.04-8.00)</td>
<td>.04</td>
<td>1.47 (0.34-6.29)</td>
</tr>
<tr>
<td>SCC</td>
<td>7.81 (3.94-15.60)</td>
<td>&lt;.001</td>
<td>1.51 (0.69-3.28)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3.13 (0.42-22.69)</td>
<td>.26</td>
<td>2.73 (0.36-20.83)</td>
</tr>
</tbody>
</table>

### Abbreviations:
- alloHCT, allogeneic hematopoietic cell transplantation
- BCC, basal cell carcinoma
- HR, hazard ratio
- SCC, squamous cell carcinoma
- * Designates covariates included in the multivariate risk modeling.
- c Documented clinically before alloHCT.
- a Includes SCC and BCC.
patients determined to be at high risk for keratinocyte carcinoma after alloHCT may benefit from early evaluation and aggressive management of baseline photodamaged skin with field-directed therapies before transplant.28

This study confirms the association of increasing age, chronic lymphocytic leukemia, chronic GVHD, and RI/NMA conditioning regimens with the development of keratinocyte carcinoma after alloHCT.2-6,8,9,13,29 The association of age with keratinocyte carcinoma may be bimodal, with studies reporting increased risk in children and older adults.4,5 However, we could not assess the association of young age with keratinocyte carcinoma because we only included adults older than 18 years. The association between chronic GVHD and SCC was particularly robust, confirming previous studies reporting a strong association between chronic GVHD and SCC after alloHCT.4,6,9,29

Interestingly, cumulative duration of immunosuppression and chronic GVHD involving the skin were both associated with keratinocyte carcinoma after alloHCT in univariate but not multivariate analyses. Of note, the observed opposing effects for cyclosporine and tacrolimus on BCC risk in univariate analyses may reflect interactions with unmeasured confounding variables. Unlike recipients of solid organ transplants who experience prolonged immunosuppression, alloHCT recipients typically experience shorter courses of immunosuppression predominantly associated with treatment of chronic GVHD.5,29 Immunosuppression is strongly associated with keratinocyte carcinoma in the general population, solid organ transplant recipients, and alloHCT recipients treated with azathioprine-based regimens for longer than 24 months, and chronic skin inflammation increases keratinocyte carcinoma risk in nonhealing ulcers and discoid lupus erythematosus.8,10,11,30-32 Further studies are necessary to elucidate the direct and indirect mechanisms associated with immunosuppression and chronic skin inflammation due to chronic GVHD, contributing to keratinocyte carcinoma development after alloHCT.

Conditioning regimens consisting of RI/NMA are advantageous for older patients who may not tolerate traditional myeloablative regimens. Older adults have greater baseline keratinocyte carcinoma risk than younger adults, and RI/NMA conditioning regimens are hypothesized to be more carcinogenic than myeloablative regimens because genetically damaged cells may be eliminated.33,34 Additional investigation is also required to characterize how the increasing use of RI/NMA conditioning regimens is changing the incidence of keratinocyte carcinoma in contemporary cohorts of alloHCT recipients. In contrast to prior studies, we did not find an association between TBI and BCC risk or between cumulative duration of voriconazole exposure and SCC risk after alloHCT.2-4,6,12,35 The risk of BCC after TBI is highest in younger patients, and it appears that no additional risk is observed for HCT recipients older than 40 years.5 The fact that 663 patients (76.0%) in our Mayo Clinic cohort were older than 40 years may help explain why we did not observe an increased BCC risk in patients receiving TBI. In addition, exposure to the photosensitizing agent voriconazole may increase SCC risk after alloHCT, but possibly only for anatomical sites with higher ambient UV radiation exposure.35,36 The risk associated with voriconazole exposure in solid organ transplant recipients is diminished when controlling for sun exposure, which may also help explain why no independent association was found in our analyses controlling for clinically photodamaged skin documented before transplant.37

Limitations

Limitations of this study include its retrospective design, limited statistical power in particular when analyzing SCC and BCC individually, surveillance bias resulting in increased screening and detection of keratinocyte carcinoma, and analysis of alloHCT recipients from a single tertiary care medical center for the discovery cohort, which may not be representative of the general population undergoing alloHCT. We also could not assess the clinical severity of photodamaged skin, and there may be heterogeneity in the assessments of photodamaged skin and Fitzpatrick skin types between dermatologists. In addition, while our use of stepwise logistic regression modeling is a generally conservative strategy, other model-building strategies may have yielded different results.38

The follow-up of our cohort was also shorter than that of prior series of alloHCT recipients, which limits our analysis of the cumulative duration of immunosuppression. Some transplant-associated risk factors also change over time (eg, type and duration of immunosuppression), which makes it difficult to translate these moving targets to clinical practice. Finally, previous cohorts of alloHCT recipients included younger patients receiving myeloablative conditioning regimens, whereas our cohort consisted of relatively older patients receiving a greater proportion of RI/NMA conditioning regimens. As such, the observed predominance of host-associated risk factors may be influenced by the above differences between our cohort and previously published cohorts.

Conclusions

As overall survival after alloHCT continues to improve, long-term survivors are at risk for developing late complications, including an increased incidence of keratinocyte carcinoma that does not plateau over time.14 Consensus-based recommendations, adopted from evidence-based skin cancer screening guidelines for the general population, include routine skin cancer screening for alloHCT recipients and referral to dermatologists for management of skin lesions that cause concern.39-41 We recommend establishing baseline keratinocyte carcinoma risk in all patients eligible for alloHCT, but acquiring a greater proportion of RI/NMA conditioning regimens. As such, the observed predominance of host-associated risk factors may be influenced by the above differences between our cohort and previously published cohorts.

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ARTICLE INFORMATION

Accepted for Publication: February 6, 2020.
Published Online: April 8, 2020.

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Conflict of Interest Disclosures: Dr Scott reported receiving grants from the American Society for Dermatologic Surgery during the conduct of the study. Dr Baum reported receiving grants from the Dermatology Foundation during the conduct of the study. Dr Hashmi reported honoraria from Novartis International AG, Pfizer, Inc, Janssen Pharmaceutica, and Mallinckrodt Pharmaceuticals outside the submitted work. Dr Gerstenblith reported receiving grants from the Fowler Family Foundation, Cleveland Foundation, and the National Institutes of Health outside the submitted work. No other disclosures were reported.

Funding/Support: This study was supported by a Cutting Edge Research Grant from the American Society for Dermatologic Surgery.

Role of the Funder/Sponsor: The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentations: This paper was presented at the American College of Mohs Surgery Annual Meeting (May 3, 2018, Chicago, IL) and the American Society for Dermatologic Surgery Annual Meeting (October 12, 2018, Phoenix, AZ).

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