Original Investigation

Skin Cancer Risk in Hematopoietic Stem-Cell Transplant Recipients Compared With Background Population and Renal Transplant Recipients
A Population-Based Cohort Study

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IMPORTANCE While a high risk of nonmelanoma skin cancer is well recognized in solid-organ transplant recipients, the risk of skin cancer in hematopoietic stem-cell transplant (HSCT) recipients has not been extensively studied.

OBJECTIVE To determine the risk of cutaneous cancer in HSCT recipients and compare it with the risk in renal transplant recipients (RTRs) and individuals who have not received any transplant.

DESIGN, SETTING, AND PARTICIPANTS A nationwide population-based cohort study from the Danish National Hospital Register including 3302 patients who underwent HSCT (1007 allogeneic, 2295 autologous) from 1999 through 2014, 4789 RTRs from 1976 through 2014, and 10 age- and sex-matched nontransplanted individuals for each of the groups from the background population. Person-years at risk were calculated from the time of study inclusion until first cutaneous cancer. To compare the risk of skin cancer between transplant recipients and background population, we used a stratified proportional hazard regression model for hazard ratio (HR) estimations. By use of the cumulative incidence, we estimated 5- and 10-year risks of skin cancers. All RTR and HSCT recipients were treated and followed up in specialized hospital departments in Denmark (total population 5.7 million).

MAIN OUTCOMES AND MEASURES Primary outcomes were time to first appearance of basal cell carcinoma (BCC), squamous cell carcinoma (SCC), or malignant melanoma (MM) and comparative risk estimates of cutaneous cancers in HSCT recipients and RTRs. The hypothesis was tested during data collection.

RESULTS Allogeneic HSCT recipients had an increased risk of BCC, SCC, and MM, with respective HRs of 3.1 (95% CI, 1.9-5.2), 18.3 (95% CI, 4.1-81.8), and 5.5 (95% CI, 1.7-17.7) compared with the background population. Compared with RTRs, allogeneic HSCT recipients had a 3-fold higher risk of MM. The risk of BCC after allogeneic HSCT was seen only in patients conditioned with total-body irradiation (HR, 3.9 [95% CI, 2.6-6.8]). The risk of BCC was similar for allogeneic HSCT recipients and RTRs, while the risk of SCC was highest for RTRs. Autologous HSCT recipients had no increased risk of skin cancer.

CONCLUSIONS AND RELEVANCE Allogeneic HSCT recipients have an increased risk of BCC, SCC, and MM. Total-body irradiation was a major determinant for BCC. Our findings indicate the relevance of dermatologic follow-up in HSCT recipients.

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mmunosuppressed patients are at increased risk of developing cutaneous cancer. This is well known for solid-organ transplant recipients undergoing lifelong immunosuppressive therapy, who are at a highly increased risk of nonmelanoma skin cancer (NMSC). In consequence, posttransplant dermatologic examination is established for this patient group.

Patients undergoing hematopoietic stem-cell transplantation (HSCT) similarly experience immunosuppression caused by irradiation and treatment with chemotherapy used for conditioning. Hematopoietic stem-cell transplantation is a potentially curative treatment for malignant and nonmalignant hematopoietic diseases and can be classified according to the donor source. In autologous HSCT, the patient’s own cells are collected and reinfused after administration of myeloablative doses of chemotherapy whereas in allogeneic HSCT, the hematopoietic cells derive from an HLA-matched donor. Allogeneic HSCT is further subdivided according to the type of pretransplant conditioning administered. In myeloablative HSCT, the host’s hematopoiesis is completely eradicated with chemotherapy, which is often supplemented with total-body irradiation (TBI). In nonmyeloablative HSCT, the intensity of the conditioning regimen is reduced, permitting allogeneic engraftment without complete ablation of the host.

With modern HSCT, the nonrelapse mortality rate has been reduced to approximately 25%, and overall mortality to below 50%, representing a marked reduction compared with 10 years ago. Understanding the long-term complications in HSCT recipients is therefore of interest.

An overall increased risk of solid cancer, including skin cancer, has been reported for recipients of allogeneic HSCT. While solid-organ transplant recipients predominantly develop squamous cell carcinoma (SCC), malignant melanoma (MM) appears to be among the most frequent secondary cancers following HSCT. The risk of basal cell carcinoma (BCC) in HSCT recipients has not been investigated in population-based cohort studies because few countries include BCC in their cancer registries. In autologous HSCT recipients, an increased risk of secondary cancer has been reported, but to our knowledge, no studies have focused on the risk of cutaneous cancer. In general, there is a lack of work focusing on skin cancer after HSCT, and no studies to our knowledge have compared the risk of cutaneous cancer between HSCT recipients and solid-organ transplant recipients.

In this large-scale, nationwide, population-based cohort study, we aim to compare the risks of the most common cutaneous cancers (SCC, BCC, and MM) in HSCT recipients and renal transplant recipients (RTRs) with risk in the background population. Furthermore, we compare the risk of skin cancer between allogeneic HSCT recipients and RTRs to investigate whether future efforts in secondary prevention similar to those undertaken with solid-organ transplant recipients should be established following allogeneic HSCT.

Methods

Data Sources
We used 4 national registries as data sources following approval from the Danish Data Protection Agency, journal number 2007-58-0015. According to Danish law, no human participant committee approval is required for register-based studies.

The Danish population consists of 5.7 million inhabitants, and each citizen carries a unique 10-digit Central Person Registration number given at birth or at time of immigration. We used this number to track individuals in the following registries and to link the following data sources: The Danish National Hospital Register contains information on all nonpsychiatric hospital admissions from 1977 and on outpatient clinics from 1995. The information registered for each contact includes date of admission and discharge, hospital department, and up to 20 discharge diagnoses assigned by physicians and coded according to the International Classification of Diseases, Eighth Revision (ICD-8) through 1993 and the ICD-10 from 1994 to the present. The registry also contains information on surgical and nonsurgical procedures coded according to SKS (Sygehusvæsnets Klassifikationssystem [hospital classification of disease]), which represents a compilation of International, Nordic, and Danish classifications based on the international ICD-10 and the Nordic Classification of Surgical Procedures. Data on transplantation procedure, transplantation date, conditioning regimen, and TBI exposure were collected from this register.

The Danish Civil Registration System established in 1968 contains demographic data and vital status on all Danish citizens. From this register we collected data on birth, sex, loss to follow-up, and date of death.

The Danish Cancer Registry has recorded data on cancer diagnoses in Denmark since 1943. Cancers are classified according to the ICD-7 from 1943 through 1977 and ICD-10 from 1978 through 2006. At first diagnosis of cancer and at the time of change of initial cancer diagnosis, clinical hospital departments, departments of pathology, and general practitioners report to the registry. Reporting is mandatory, and the proportion of morphologically verified tumors is 89%. From this register we collected data on skin cancer diagnosis.

Inclusion and Exclusion Criteria
We identified as index patients all patients who underwent an allogeneic or autologous HSCT from 1999 through 2013 or renal transplantation from 1976 through 2013 from the Danish National Hospital Register according to the SKS codes. For every index patient, we randomly selected 10 age- and sex-matched nontransplanted individuals from the background population for the comparison cohort. Both transplant recipients and nontransplant individuals had to be alive and living in Denmark at the time of transplantation of the index patient. Furthermore, transplant recipients and individuals from the comparison cohort were excluded if they received a skin cancer diagnosis prior to the index date. Moreover, index patients were excluded if they received additional HSCT or a renal transplant prior to the index date.

Statistical Analysis
The primary study outcomes were time to first appearance of skin cancer (BCC, SCC, or MM). Person-years at risk were calculated as the time between study inclusion and the occurrence of the event of interest.
rence of 1 of the following events: date of first cutaneous cancer, date of death, date of second transplantation, loss to follow-up, or December 31, 2013. To compare the risk of skin cancer between transplant recipients and the comparison cohort, we used a stratified proportional hazard regression model for the hazard ratio (HR) estimations in accordance with the matched design. We repeated our analyses in strata defined by conditioning regimen.

The 5- and 10-year risks of skin cancer were estimated by the use of the cumulative incidence function, in which death was considered a competing risk.17 We compared the risk of skin cancer between allogenic HSCT recipients and RTRs by the use of a Cox regression analysis, adjusting for age and sex, to compare the risk of skin cancer between these 2 patient groups differing in transplantation type but similar in age at the time of transplantation.

Results

We identified 1007 allogeneic HSCT recipients, 2295 individuals who underwent autologous HSCT, and 4789 RTRs. For each allogeneic HSCT recipient, autologous HSCT recipient, and RTR, we identified 10 070, 22 950, and 47 890 correspondingly matched persons, respectively, from the background population. For descriptive data, see Table 1.

Cutaneous cancer was seen in 2.6% of allogeneic HSCT recipients: 69.2% BCC, 15.4% SCC, and 15.4% MM. In the age- and sex-matched background population, cutaneous cancer was seen in 0.9%. Among patients who had received autologous HSCT, 2.0% developed skin cancer: 76.1% BCC, 8.7% SCC, and 15.2% MM. In the matched background population cutaneous cancer appeared in 3.6%. In RTRs, skin cancer was seen in 14.0%: 57.1% BCC, 39.2% SCC and 3.7% MM; and in the matched background population, 5.8% developed skin cancer.

Increased Risk of BCC and SCC in Allogeneic HSCT Recipients and RTRs

The risk of BCC was increased for allogeneic HSCT recipients and RTRs, with HRs of 3.1 (95% CI, 1.9-5.2; P < .001) and 5.9 (95% CI, 5.3-6.6; P < .001), respectively, compared with their background population. For detailed data, see Table 2.

For autologous HSCT, the HR for BCC was 1.4 (95% CI, 0.99-2.0; P = .79) compared with the background population.

Table 1. Characteristics of the Transplant Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Allogeneic HSCT Recipients (n = 1007)</th>
<th>Autologous HSCT Recipients (n = 2295)</th>
<th>Renal Transplant Recipients (n = 4789)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, No. (%)</td>
<td>618 (61.4)</td>
<td>1429 (62.3)</td>
<td>2944 (61.5)</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>43.0 (20.1-57.6)</td>
<td>57.9 (48.4-63.3)</td>
<td>44.7 (32.5-54.4)</td>
</tr>
<tr>
<td>Person-years of observation</td>
<td>3743.8</td>
<td>8842.9</td>
<td>45 911.3</td>
</tr>
<tr>
<td>Median follow-up, y</td>
<td>2.4</td>
<td>3.0</td>
<td>7.7</td>
</tr>
<tr>
<td>Transplantation year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before 2000</td>
<td>0</td>
<td>0</td>
<td>2702 (56.4)</td>
</tr>
<tr>
<td>2000 to 2009</td>
<td>565 (56.1)</td>
<td>1488 (64.8)</td>
<td>1364 (28.5)</td>
</tr>
<tr>
<td>2010 or later</td>
<td>442 (43.9)</td>
<td>807 (35.2)</td>
<td>723 (15.1)</td>
</tr>
<tr>
<td>TBI</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>328 (32.6)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Myeloablative HSCT</td>
<td>632 (62.8)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Nonmyeloablative HSCT</td>
<td>375 (37.2)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: HSCT, hematopoietic stem-cell transplantation; IQR, interquartile range; NA, not applicable; TBI, total-body irradiation.

Table 2. Absolute and Relative Risk of BCC Among Transplant Recipients Compared With the Nontransplant Background Population

<table>
<thead>
<tr>
<th>Transplant Type</th>
<th>BCC Cases, No.</th>
<th>HR (95% CI)</th>
<th>P Value</th>
<th>Absolute Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transplants</td>
<td>Background</td>
<td></td>
<td>5-Year</td>
</tr>
<tr>
<td>Allogeneic HSCT (n = 1007)</td>
<td>18</td>
<td>82</td>
<td>3.1 (1.9-5.2)</td>
<td>.001</td>
</tr>
<tr>
<td>Myeloablative (n = 632)</td>
<td>7</td>
<td>26</td>
<td>4.0 (1.8-9.3)</td>
<td>.001</td>
</tr>
<tr>
<td>Nonmyeloablative (n = 375)</td>
<td>11</td>
<td>56</td>
<td>2.9 (1.5-5.5)</td>
<td>.002</td>
</tr>
<tr>
<td>TBI (n = 679)</td>
<td>16</td>
<td>62</td>
<td>3.9 (2.6-6.8)</td>
<td>.001</td>
</tr>
<tr>
<td>No TBI (n = 328)</td>
<td>2</td>
<td>20</td>
<td>1.3 (0.3-5.4)</td>
<td>.76</td>
</tr>
<tr>
<td>Autologous HSCT (n = 2295)</td>
<td>35</td>
<td>388</td>
<td>1.4 (0.99-2.0)</td>
<td>.07</td>
</tr>
<tr>
<td>RT (n = 4789)</td>
<td>384</td>
<td>1310</td>
<td>5.9 (5.3-6.6)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: BCC, basal cell carcinoma; HR, hazard ratio; HSCT, hematopoietic stem-cell transplant; NA, not applicable; RT, renal transplant; TBI, total-body irradiation.
TBI-based regimen (HR, 14.2 [95% CI, 2.9-70.6]; P = .001). There was a notably increased risk of SCC among RTRs, with an HR of 34.3 (95% CI, 28.0-41.9; P < .001). In contrast, autologous HSCT was not associated with increased risk of SCC (Table 3).

The 10-year risk of developing BCC in the allogeneic HSCT recipients, autologous HSCT recipients, and RTRs was 5.3% (95% CI, 2.9%-8.8%), 4.7% (95% CI, 3.2%-6.7%), and 6.9% (95% CI, 6.0%-7.9%), respectively. The 10-year risk of developing SCC was, respectively, 0.8% (95% CI, 0.3-1.9), 0.2% (95% CI, 0.1%-0.8%), and 4.8% (95% CI, 4.1%-5.7%) (Tables 2 and 3). The Figure shows the 10-year cumulative incidence estimates of BCC risk in allogeneic HSCT recipients with and without exposure to TBI, in RTRs, and in the corresponding matched background populations.

TBI Conditioning and Risk of BCC in Allogeneic HSCT Recipients

The risk of BCC development was dependent on whether allogeneic HSCT recipients were exposed to TBI. Patients who underwent allogeneic HSCT with TBI exposure as part of their conditioning regimen had a nearly 4-fold increase in BCC risk (HR, 3.9 [95% CI, 2.6-6.8]; P < .001) compared with the background population. In contrast, allogeneic HSCT recipients not exposed to TBI had no increased risk of BCC (HR, 1.3 [95% CI, 0.3-5.4]; P = .76) compared with the background population (Table 2). The risk of BCC did not differ significantly in relation to whether the allogeneic regimen was myeloablative or nonmyeloablative (Table 2).

### Table 3. Absolute and Relative Risk of SCC Among Transplant Recipients Compared With the Nontransplant Background Population

<table>
<thead>
<tr>
<th>Transplant Type</th>
<th>SCC Cases, No.</th>
<th>HR (95% CI)</th>
<th>P Value</th>
<th>Absolute Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transplants</td>
<td>Background</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allogeneic HSCT (n = 1007)</td>
<td>4</td>
<td>3</td>
<td>18.3 (4.1-81.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Myeloablative (n = 632)</td>
<td>2</td>
<td>1</td>
<td>4.0 (1.8-9.3)</td>
<td>.01</td>
</tr>
<tr>
<td>Nonmyeloablative (n = 375)</td>
<td>2</td>
<td>2</td>
<td>14.7 (2.1-104.3)</td>
<td>.01</td>
</tr>
<tr>
<td>TBI (n = 679)</td>
<td>3</td>
<td>3</td>
<td>14.2 (2.9-70.6)</td>
<td>.001</td>
</tr>
<tr>
<td>No TBI (n = 328)</td>
<td>1</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Autologous HSCT (n = 2295)</td>
<td>4</td>
<td>43</td>
<td>1.4 (0.5-3.9)</td>
<td>.52</td>
</tr>
<tr>
<td>RT (n = 4789)</td>
<td>264</td>
<td>166</td>
<td>34.3 (28.0-41.9)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; HSCT, hematopoietic stem-cell transplant; NA, not applicable; RT, renal transplant; SCC, squamous cell carcinoma; TBI, total-body irradiation.

### Figure

A, Hematopoietic stem-cell transplant recipients (HSCTRs) with and without total-body irradiation (TBI) exposure vs the nontransplant background population. B, Renal transplant recipients (RTRs) vs the nontransplant background population.
Table 4. Absolute and Relative Risk of MM Among Transplant Recipients Compared With the Nontransplant Background Population

<table>
<thead>
<tr>
<th>Transplant Type</th>
<th>MM Cases, No.</th>
<th>MM Cases, No. Background</th>
<th>HR (95% CI)</th>
<th>P Value</th>
<th>Absolute Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transplants</td>
<td>Background</td>
<td></td>
<td></td>
<td>S-Year</td>
</tr>
<tr>
<td>Allogeneic HSCT (n = 1007)</td>
<td>4</td>
<td>10</td>
<td>5.5 (1.7-17.7)</td>
<td>.004</td>
<td>0.7 (0.2-1.9)</td>
</tr>
<tr>
<td>Myeloablative (n = 632)</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Nonmyeloablative (n = 375)</td>
<td>2</td>
<td>8</td>
<td>3.7 (0.8-17.5)</td>
<td>.01</td>
<td>NA</td>
</tr>
<tr>
<td>TBI (n = 679)</td>
<td>4</td>
<td>9</td>
<td>6.6 (2.0-21.3)</td>
<td>.002</td>
<td>NA</td>
</tr>
<tr>
<td>No TBI (n = 328)</td>
<td>0</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Autologous HSCT (n = 2295)</td>
<td>7</td>
<td>77</td>
<td>1.4 (0.6-3.0)</td>
<td>.44</td>
<td>0.5 (0.2-1.1)</td>
</tr>
<tr>
<td>RT (n = 4783)</td>
<td>25</td>
<td>245</td>
<td>1.8 (1.2-2.8)</td>
<td>.01</td>
<td>0.2 (0.1-0.4)</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; HSCT, hematopoietic stem-cell transplant; MM, malignant melanoma; NA, not applicable; RT, renal transplant; TBI, total-body irradiation.

**Increased Risk of MM in Allogeneic HSCT Recipients and RTRs**

Patients receiving allogeneic HSCT had an increased risk of developing MM, with an HR of 5.5 (95% CI, 1.7-17.7) 

P = .004 compared with the corresponding cohort, while no increased risk was observed for patients undergoing autologous HSCT (HR, 1.4 [95% CI, 0.6-3.0]; P = .44). The risk of developing MM was also increased for RTRs, with an HR of 1.8 (95% CI, 1.2-2.8; P = .01) compared with the matched background population (Table 4). The 10-year risk of developing MM is detailed in Table 4.

For patients undergoing allogeneic HSCT with TBI as part of the conditioning regimen, the HR of MM was 6.6 (95% CI, 2.0-21.3; P = .002) compared with the background population. No cases of MM were seen in the allogeneic HSCT recipients not exposed to TBI.

**Increased Risk of MM in Allogeneic HSCT Recipients Compared With RTRs**

The median age at time of transplantation was nearly identical for patients undergoing allogeneic HSCT and renal transplantation. The risk of developing MM was higher for allogeneic HSCT recipients, with an HR of 5.5 (95% CI, 1.7-17.7; P = .004) compared with the comparison cohort; while for RTRs, the MM risk was twice that of the comparison cohort (HR, 1.8 [95% CI, 1.2-2.8]; P = .01) (Table 4). When the risk of MM in allogeneic HSCT recipients was compared directly with the risk of MM in RTRs and adjusted for sex and age, an increased risk of MM in patients who underwent allogeneic HSCT was observed, with a HR of 3.1 (95% CI, 1.0-9.4; P = .048). The risk of MM was even higher in TBI-exposed allogeneic HSCT recipients compared with RTRs (HR, 4.0 [95% CI, 1.3-12.1]; P = .02), although with overlapping CIs. The risk of developing SCC was higher for RTRs than for allogeneic HSCT recipients, with an HR of 4.3 (95% CI, 1.6-11.5; P = .004), while the risk of BCC development was identical for allogeneic HSCT recipients and RTRs (HR, 0.9 [95% CI, 0.6-1.5]; P = .75).

**Discussion**

To our knowledge, this is the first cohort study to integrate health data from multiple comprehensive national registries to analyze the risk of developing cutaneous cancers, including BCC, in both HSCT recipients and RTRs. We found an overall increased risk of all cutaneous cancers in patients undergoing allogeneic HSCT and renal transplantation compared with the general population. Autologous HSCT was associated with a slightly higher risk of BCC compared with the background population, although the difference was not statistically significant. No increased risk of SCC or MM following autologous HSCT was observed. We demonstrated a 3-fold increased risk of MM in allogeneic HSCT recipients compared with RTRs, while RTRs had a higher risk of developing SCC. No difference in the risk of BCC development between RTRs and allogeneic HSCT recipients was observed.

A major strength of this study is the population-based cohort design. The unique Danish Civil Registration system enabled identification of a large population cohort matched on sex and age with virtually complete follow-up. Via the Danish registries, we had access to complete data on cancer diagnoses, including BCC, uncommon for most countries.

A limitation to our study was reliance on register-based discharge and cancer diagnoses without additional validation of diagnoses. Comprehensive assessment, however, has shown the cancer registry to be 95% to 98% complete and valid. A further limitation to our study was the relatively low case numbers of SCC and MM.

Our findings are consistent with previous reports on skin cancer in transplant patients, where cutaneous cancer secondary to allogeneic HSCT is primarily MM, and that for the solid-organ transplant recipients is mainly NMSC, particularly SCC. The largest study examining secondary solid cancer after allogeneic HSCT found a standardized incidence ratio of 3.5 for MM, moderately lower than the HR of 5.5 in our study. The standardized incidence ratio was not calculated for NMSC because population-based incidence rates were not available for NMSC. A study from 1997 found an overall/estimated risk of MM of 5 after allogeneic HSCT, corresponding to our findings. Ten-year cumulative incidence rates of 2.5 and 1.4 for BCC and SCC, respectively, in allogeneic HSCT were found in a retrospective cohort study of 4810 patients from Seattle without comparison with controls. We found a higher 10-year risk of BCC and a lower 10-year risk of SCC (0.3 and 0.8, respectively). Underreporting of BCC is likely the cause of the lower BCC risk observed in the American study. The overall risk...
of cancer secondary to autologous HSCT may be moderately elevated compared with the background population, but the risk of NMSC has not been investigated in a population-based cohort study, and the risk of MM has been addressed in only 1 study. While this Australian study reported excess risk for MM after autologous HSCT, we observed no evidence of increased MM risk in our cohort. In the Australian study, however, TBI was part of the conditioning regimen for some of the autologous HSCT recipients, with patients undergoing the TBI-based regimen less frequently in recent years. In Denmark, TBI is not standard for autologous HSCT, and the observed increased risk of MM in the Australian study may reflect the use of TBI in the initial part of the study period. No increased risk of NMSC was found for the autologous HSCT population.

Reasons for the difference in secondary cutaneous cancer risk among the 3 transplantation groups are likely multifactorial. One important contributor is exposure to radiotherapy. In several studies, TBI has been associated with the development of BCC and MM but not with SCC. This finding was recently confirmed in a systematic review on cutaneous malignant neoplasms in HSCT recipients. For patients undergoing allogeneic HSCT, TBI is often part of the conditioning regimen (67% in our study), whereas RTRs are not exposed to TBI. Furthermore, TBI is not part of the conditioning regimen for autologous HSCT in Denmark. We, in agreement with other studies, observed an association between TBI and risk of BCC. Allogeneic HSCT patients exposed to TBI as part of the conditioning regimen had a nearly 4-fold increase in BCC risk, whereas individuals not exposed to TBI had no increased risk of developing BCC. For MM, we observed a relationship between MM and TBI, but our study lacked statistical power, and so conclusions should be drawn with caution. No cases of MM were found in patients without TBI exposure.

It has been debated whether nonmyeloablative regimens are associated with lower risk of secondary cancer after allogeneic HSCT compared with myeloablative regimens. In our study, no statistically significant difference in risk of BCC was found when comparing myeloablative with nonmyeloablative regimens. We did not study the impact of nonmyeloablative regimens for other types of skin cancer owing to the limited number of SCC and MM cases.

Duration of immunosuppression has been associated with secondary SCCs of the skin and other organs in HSCT recipients, and one might speculate that risk of SCC is primarily associated with long-term immunosuppression: For solid-organ transplant recipients, the duration of immunosuppressive therapy is usually lifelong, whereas some HSCT recipients discontinue their immunosuppressive treatment after transplantation. Development of graft vs host disease (GVHD) prompts increased levels of immunosuppressive therapy, and GVHD has been associated with an increased risk of SCC. We did not study the relation between skin cancer and GVHD owing to the limited number of SCC cases.

The risk of MM and BCC might, to a greater degree, be driven by an initiator event such as irradiation, short-duration heavy immunosuppressive regimens, short-term high-dose UV exposure, and others. This is in agreement with BCC, and to some extent MM, being linked to radiation exposure. In contrast, little evidence supports association between SCC and irradiation. This corresponds to the impact of sun exposure, where the risk of SCC is correlated with accumulated sun exposure, whereas MM and BCC are primarily linked to sunburns. Furthermore, a general immunosuppressed state is primarily important in regard to SCC risk. For solid-organ transplant recipients, the incidence of SCC has been reported as proportional to the level of immunosuppression, and CD4 counts are significantly lower in solid-organ transplant recipients with cutaneous carcinoma than in those without.

Conclusions
With this study, we have provided an overview of skin cancer risk in the different transplantation cohorts by comparing the risk of cutaneous cancer in these groups. The risk of developing SCC is higher for RTRs than for HSCT recipients, and there is a similar risk of developing BCC. However, there is a higher risk of MM for allogeneic HSCT recipients, a disease with a much higher mortality rate than NMSC.

In Denmark, solid-organ transplant recipients are regularly screened for skin cancer at outpatient dermatology clinics. Conversely, allogeneic HSCT recipients are not systematically examined for cutaneous cancer. In light of our findings, future efforts in secondary prevention following allogeneic HSCT should be intensified and particularly aimed at TBI-exposed individuals. Furthermore, studies examining prognosis of skin cancer in HSCT recipients are needed.

ARTICLE INFORMATION
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REFERENCES


