Review

Cutaneous Malignant Neoplasms in Hematopoietic Cell Transplant Recipients
A Systematic Review

Jennifer L. DePry, DO; Ritva Vyas, MBChB, FRACP; Hillard M. Lazarus, MD; Paolo F. Caimi, MD; Meg R. Gerstenblith, MD; Jeremy S. Bordeaux, MD, MPH

IMPORTANCE Hematopoietic cell transplantation has increased the survival of patients with several types of malignant hematologic disease and hematologic disorders; however, these patients have an increased risk of posttransplant cutaneous malignant neoplasms. Physicians should be aware of associated risk factors to provide appropriate patient screening and long-term care.

OBJECTIVE To identify the incidence and risk factors for cutaneous malignant neoplasms following hematopoietic cell transplantation.

EVIDENCE REVIEW A systematic review was conducted using Medline and Cochrane databases from January 1995 to December 2013. Retrospective and prospective reviews containing at least 100 patients who underwent hematopoietic cell transplantation reporting skin cancer as a primary outcome were included. Information regarding the entire cohort, data for the subset who developed cutaneous malignant neoplasms, and cutaneous malignant neoplasm risk factors were extracted from included articles. The level of evidence for each study was assessed using the Strength of Recommendation Taxonomy scale.

FINDINGS Patients who underwent hematopoietic cell transplantation had an increased risk of squamous cell carcinoma, basal cell carcinoma, and melanoma. Factors such as primary disease, chronic graft-vs-host disease, prolonged immunosuppression, radiation exposure, light skin color, sex, and T-cell depletion are risk factors for cutaneous malignant neoplasms.

CONCLUSIONS AND RELEVANCE Given the increased risk of cutaneous malignant neoplasms in hematopoietic cell transplant recipients, this population should be educated on skin self-examination and pursue regular follow-up with dermatologists.

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Author Affiliations: Department of Dermatology, University Hospitals Case Medical Center, Cleveland, Ohio (DePry, Vyas, Gerstenblith, Bordeaux); Case Comprehensive Cancer Center, Cleveland, Ohio (Vyas, Lazarus, Caimi, Gerstenblith, Bordeaux); Division of Hematology and Oncology, Department of Internal Medicine, University Hospitals Case Medical Center, Cleveland, Ohio (Lazarus, Caimi).

Corresponding Author: Jennifer L. DePry, DO, Department of Dermatology, University Hospitals Case Medical Center, 11100 Euclid Ave, Lakeside Third Floor, Cleveland, OH 44106 (jennifer.depry@uhhospitals.org).

The introduction of hematopoietic cell transplantation (HCT) has increased the survival of patients with several cancers and hematologic disorders. As survival continues to improve, the associated long-term risks, particularly the increased incidence of second primary solid tumors and malignant hematologic diseases, are becoming more apparent.

The increased risk of skin cancer among solid-organ transplant recipients (SOTRs) is well documented.[1-3] Unlike SOTRs, HCT recipients tend to have a short course of immunosuppression but nonetheless develop subsequent primary malignant neoplasms. In addition to immunosuppression, several factors contribute to the increased risk of tumors including age at transplantation, primary disease type, and graft-vs-host disease (GVHD).[4-6]

The 3 main categories of post-HCT malignancies are solid tumors, malignant hematologic diseases, and lymphoproliferative disorders.[7] Most solid tumors have a greater latency after transplantation than lymphoproliferative disorders and therapy-induced hematologic disorders.[8,9] Of the solid tumors, the risk is particularly elevated for cutaneous and oral mucosal malignant neoplasms. To further evaluate these risk factors and the incidence of cutaneous neoplasms among HCT recipients, we conducted a systematic review using studies from Medline and Cochrane databases.

Methods

Data Search

We searched Medline (PubMed) and the Cochrane Database of Systematic Reviews for articles in English published from January 1, 1995, through December 31, 2013, and from January 1, 2005, through December 31, 2013, respectively. For Medline, the following search

terms were used: "stem cell transplant" and "bone marrow transplant" combined with "skin malignancy," "squamous cell carcinoma," "basal cell carcinoma," "melanoma," "Merkel cell carcinoma," "keratoacanthoma," and "Kaposi's sarcoma." For the Cochrane database, the search terms "stem cell transplant" OR "bone marrow transplant" were combined with the "AND" command for the terms "skin malignancy," "squamous cell carcinoma," "basal cell carcinoma," "melanoma," "Merkel cell carcinoma," "keratoacanthoma," and "Kaposi's sarcoma."

Inclusion and Exclusion Criteria

Retrospective and prospective studies were included if skin cancer was analyzed as a primary outcome and the cohort included more than 100 HCT recipients. Studies were excluded if the data from a later study included the same individuals and the data were analyzed for the same outcomes. In this case, only the updated data were used. Studies were also excluded if the total number of patients who underwent HCT could not be determined. If the total number of HCT recipients who developed cutaneous malignant neoplasms or the total number of cutaneous malignant neoplasms observed in HCT recipients could not be determined, the study was also excluded. Studies in which head and neck malignant neoplasms or oral malignant neoplasms were evaluated, but the location as to cutaneous or mucosal surface was not specified, were excluded.

Study Selection and Data Extraction

The titles and abstracts were reviewed; if the article was deemed relevant, the entire article was reviewed as well. Information regarding the entire cohort, data for the subset who developed cutaneous malignant neoplasms, and cutaneous malignant neoplasm risk factors identified by the study were extracted from the selected articles.

Evaluation of the Quality of Evidence

The level of evidence for each study was assessed using the Strength of Recommendation Taxonomy (SORT) scale published by Ebell et al.[10] The quality of each study was rated as level 1, 2, or 3.

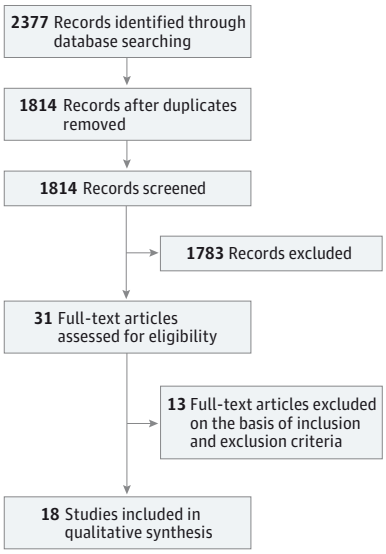
Results

Of the 2377 studies identified on Medline and in the Cochrane databases, 18 met inclusion criteria (**Figure**). The 14 cohort, 1 case-control, and 2 combined nested case-control and cohort studies, as well as 1 randomized clinical trial, all met an evidence level of 2 based on SORT criteria (**Table 1**).

Incidence and Risk

Skin cancers among HCT recipients were observed in 14 of 18 articles. The cohort demographic and clinical characteristics in the 18 selected studies are listed in Table 1. The demographic and clinical characteristics and risk factors identified in patients who developed cutaneous malignant neoplasms are listed in **Table 2**. Cutaneous malignant neoplasms were one of the most common types of second malignant neoplasms reported, accounting for 0% to 58.5% of the total tumors observed, and some studies reported patients with multiple cutaneous malignant neoplasms.[4,5,8,15,18,19] Squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and melanoma were the most common cutaneous malignant neoplasms reported, and less common types included myxofibrosarcoma, Kaposi sarcoma, and malignant fibrous histiocytoma.[6,14,22]

Figure. Flowchart of Selected Studies for Systematic Review



The median interval to diagnosis from the time of HCT was 7.3 to 9.4 years for BCC[4,8,14,19] and 2.1 to 7.0 years for SCC.[4,6,8,11,14,19] Of the 18 melanomas reported in the Rizzo et al[6] study, half occurred relatively early, between 1 and 4 years from the time of transplantation.

The 20-year cumulative incidence was 6.5% for BCC and 1.1% and 3.4% for all types of SCC and cutaneous SCC, respectively.[4,11] In 3 studies, the observed to expected ratios of melanoma in HCT recipients were between 3.5 and 8.3 relative to general population age- and sex-matched controls.[6,7,18]

Primary Disease

Two studies showed that primary disease may be associated with the development of cutaneous malignant neoplasms. In the first study, patients with a primary diagnosis of leukemia, lymphoma, or malignant marrow disease seemed to have a higher risk of BCC (univariate hazard ratio, 2.4; $P = .02$), but not SCC, relative to patients with immunologic, metabolic, and nonmalignant disease, as well as hematologic or marrow failure.[4] Although the second study did not separate SCC on the basis of location, the authors reported leukemia and severe aplastic anemia to be the predominant primary disease for patients who developed all types of SCC.[11]

Graft Source and Graft Manipulation

Some studies suggested that the graft source and graft manipulation were risk factors for cutaneous malignant neoplasm development. In Rizzo et al,[6] T-cell depletion was a significant risk factor for melanoma (relative risk [RR], 3.5; $P < .05$) but not for cutaneous SCC. In the same study, 2 or more HLA antigen mismatches were not a risk factor in melanoma or cutaneous SCC development.[6] Leisenring et al[4] found no association between related or unrelated donor type with the development of SCC or BCC.

Table 1. Cohort Demographic and Clinical Characteristics

Source	Cohort Size	Primary Skin Cancers, No., or Patients With Primary Skin Cancers, No.	Cutaneous Malignant Neoplasms of Solid Tumors, No. (%)	Age at HCT, Median (Range), y	Male/ Female, %	Primary Diseases	Type and Source of Transplant	Years Studied	Follow-up, Median (Range), y	Quality of Evidence[a]
Rizzo et al,[6] 2009[b]	28 874	43 Cancers[c]	43/189 (22.8)	27	59.3/40.7	ALL, ANLL, CML, other leukemia, NHL, HL, MM, other malignant neoplasm, AA, MDS, MPD, HGB, other	Allogeneic BM	1964-1994 (CIBMTR) 1969-1996 (FHCRC)	6641 > 5 y, 1985 > 10 y, 378 > 15 y	2
Curtis et al,[11] 2005[b]	24 011	41 Cancers[c]	41/183 (22.4)	(3.5-61.3)	42/58	ALL, ANLL, CML, lymphoma, MM, AA, Fanconi anemia, HGB	Allogeneic or syngeneic BM	1964-1996	(0.1-26.4)	2
Schwartz et al,[12] 2009[b]	6306	282 Cancers[d]	Other solid tumors not reported	(0-65)	54.8/45.2	Not reported	Autogeneic or allogeneic	1969-2006	(100 d to 36.2 y)	2
Leisenring et al,[4] 2006[b]	4810	211 Patients	Total cutaneous malignant neoplasms not reported	31.3 (0.3-72.6)	57/43	ALL, AML, CLL, CML, HD, MDS, MM, NHL, AA, HGB MPD, other malignant neoplasm, other	Allogeneic	1969-2003	9.7 (0.4-33.5)	2
Baker et al,[7] 2003	3372	27 Cancers	27/62 (44)	24 (0.1-67)	57/43	CML, AML, ALL, NHL, AA, MDS, HD, other malignant neoplasm, other	Allogeneic or autogeneic	1974-2001	5 (0.5-25)[2]	2
Bhatia et al,[13] 2001[e]	2129	9 Cancers	9/29 (31)	33.9 (1.5-71.5)	57/43	AML, NHL, CML, ALL, HD, AA	Allogeneic or autogeneic BM	1976-1998	3.3 (0.1-21.1)	2
Yokota et al,[14] 2012	2062	6 Cancers	6/30 (20)	36 (7-68)	59.4/40.6	AML, CML, ALL, MDS, lymphoma, AA, MM, MPD, other malignant neoplasm, other	Allogeneic BM, PB, or CB	1984-2005	3.3 (0.2-21.9)	2
Kolb et al,[5] 1999[f]	1036	14 Cancers	14/50 (28)	21 (1-51.9)	56/44	AML, MDS, ALL, CML, AA, other	Allogeneic, syngeneic, autogeneic BM	Not reported	10.7 (5-22.1)	2
Gallagher et al,[8] 2007	926	12 Cancers	12/30 (40)	39 (12-65)	55/45	AML, CML, ALL, MDS, MM, other malignant neoplasm, other	Allogeneic or syngeneic BM or PB	1985-2003	1.8 (0-19.2)	2
Krishnan et al,[15] 2013[e]	841	31 Cancers	31/53 (58)	56 (18-77)	61/39	Not reported	Autogeneic PB	1989-2009	3.4 (0.3-19.9)	2
Shimada et al,[16] 2005	809	0	0/19 (0)	34 (15-70)	60/40	CML, AML, ALL, NHL, AA, MDS, HL, MM, other malignant neoplasm, other	Allogeneic, autogeneic, or syngeneic	1981-2000	5.3 (1-19.9)	2
Au et al,[17] 2004	615	0	0/9 (0)	35.5 (18-65)	58.6/41.4	Not reported	Allogeneic	1990-2003	3.42 (1-164 mo) in 371 survivors	2
Brown et al, 2005[18]	605	44 Patients	Total cutaneous malignant neoplasms not reported	44	58/42	B-cell NHL	Autogeneic BM	1982-1997	9.5	2
Hasegawa et al,[19] 2005	557	9 Cancers	9/31 (29)	(0-15)	55.5/44.5	CML, AML, ALL, other	Allogeneic BM	1970-1993	(8-32)	2
Borgmann et al,[20] 2008	490[g]	1 Cancer[h]	1/12 (8.3)	(0-18)	55.5/44.5	Non-B ALL	Allogeneic or autogeneic	1983-2001	13.1	2
Friedrichs et al,[21] 2010[e]	176	3 Cancers[h]	3/13 (23)	37 (19-58)	54.5/45.5	AML, CML, ALL, MDS	Allogeneic BM or PB	1995-1999	9.3	2
Oddou et al,[22] 1998	171	0	0/5 (0)	38 (11-61)	62/38	HD, lymphoma	Autogeneic BM	1985-1995	4.3	2
Chen et al,[23] 2011	170	0	0/8 (0)	31 (15-68)	57.6/42.4	CML, AML, ALL, SAA, NHL	Allogeneic BM or PB	1984-2004	14.1 (5.1-23.3)	2

Abbreviations: AA, aplastic anemia; ALL, acute lymphocytic leukemia; ANLL, acute nonlymphocytic leukemia; BM, bone marrow; CB, cord blood; CIMBTR, Center for International Transplant Research; FHCRC, Fred Hutchinson Cancer Research Center; HCT, hematopoietic cell transplant; HGB, hemoglobinopathies; HL, Hodgkin lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPD, myeloproliferative disorders; NHL, non-Hodgkin lymphoma; PB, peripheral blood.

[a] According to the SORT (Strength of Recommendation Taxonomy) criteria published by Ebell et al.[10]

[b] Studies including patients from FHCRC.

[c] Excluded BCC and in situ malignant neoplasms in further analysis.

[d] Only reported BCC, excluded all others.

[e] Included patients from City of Hope hospital.

[f] European group for blood and marrow transplantation.

[g] Excluding patients who did not have an HCT.

[h] Excluding 1 SCC because site was unknown.

Table 2. Demographic and Clinical Characteristics and Risk Factors Identified in Patients Who Developed Cutaneous Squamous Cell Carcinoma (SCC), Basal Cell Carcinoma (BCC), and Melanoma After Hematopoietic Cell Transplantation (HCT)

Source	Skin Cancers, No., or Patients With Skin Cancer, No.	Male/Female, %	Age at Transplantation, Median (Range), y	Primary Diseases	Interval to Diagnosis, Median (Range), y	Cumulative Incidence Specific to Each Skin Cancer (Other Risk Measures)	Risk Factors Identified
Squamous Cell Carcinoma[a]							
Leisenring et al,[4] 2006[b]	53 Patients	64/36 (skin and mucosal SCC)	41.6 (6.8-71.4) (skin and mucosal SCC)	Hematologic/marrow failure (10), malignant hematologic disease (84), other malignant neoplasm (1) (skin and mucosal SCC)	6.3 (0.3-24.8) (skin and mucosal)	3.4% at 20 y (skin and mucosal)	Acute GVHD, chronic GVHD, younger age at transplantation (<10 y) (skin and mucosal)
Rizzo et al,[6] 2009	19 Cancers						Chronic GVHD, male sex
Curtis et al,[11] 2005[b]	19 Cancers	72/28 (all SCC cases)	26.5 (3.5-61.3) (all SCC cases)	ALL (6), ANML (15), CML (14), lymphoma/MM (1), AA (17), FA (4), HGB (1) (all SCC cases)	7.0 (0.9-22.9) (all SCC cases)	1.1% at 20 y (all SCC cases)	Combination of azathioprine + cyclosporine + steroids (all cases SCC), therapies containing azathioprine, long duration of immunosuppression, chronic GVHD
Hasegawa et al,[19] 2005	4 Cancers	50/50	33.6	CML (2), NHL (1), AA (1)	4.37		
Gallagher et al,[8] 2007	4 Cancers	25/75	49	CML (1), AML (1), MDS (1) NHL (1)	2.1		
Yokota et al,[14] 2012	1 Cancer	0/100	46	CML	1.6		
Basal Cell Carcinoma[c]							
Schwartz et al,[12] 2009	282 Cancers						TBI with greatest risk for youngest ages (<10 y) at transplant and no excess risk for age >40 y at transplant, light skin color for patients who had not undergone TBI, chronic GVHD in non-TBI patients
Leisenring et al,[4] 2006	201 Cancers	58/42	38.1 (2.9-71.3)	Hematologic/marrow failure (7), hematologic cancer (150), other malignant neoplasm (1)	7.9 (0.5-30.2)	6.5% at 20 y	TBI, light skin color, chronic GVHD, younger age at transplantation (<10 y), leukemia/lymphoma/blood or malignant marrow disease as primary diagnosis
Gallagher et al,[8] 2007	8 Cancers	50/50	41	CML (3), ALL (1), AML (1), MDS (1), MM (1), NHL (1)	7.6		
Hasegawa et al,[19] 2005	5 Cancers	100/0	39.8	ALL (2), CML (2), NHL (1)	7.3		
Yokota et al,[14] 2012	3 Cancers	0/100	40 (17-50)	AML (2), ALL (1)	8.4 (7.1-17.6)		
Borgmann et al,[20] 2008	1 Cancer	0/100	7.8	ALL	20.3		
Melanoma[d]							
Rizzo et al,[6] 2009	18 Cancers[e]				1-4 y group (<1 to >10 y)	(O:E, 3.47, EAR, 1.5)	T-cell depletion, TBI, short latent period (<1 y), female sex
Curtis et al,[11] 2005	22 Cancers						
Baker et al,[7] 2003	8 Cancers					(O:E, 8:0.96, SIR, 8.3 (95% CI, 3.6-15.1), EAR, 6.7)	
Brown et al,[18] 2005	5 Cancers					(O:E, 5:0.85)	
Yokota et al,[14] 2012	1 Cancer	100/0	51	NHL	2.1		

Abbreviations: AA, aplastic anemia; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; ANLL, acute nonlymphocytic leukemia; CML, chronic myelogenous leukemia; EAR, excess absolute risk; FA, Fanconi anemia; GVHD, graft-vs-host disease; HGB, hemoglobinopathies; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; O:E, observed to expected; SIR, standardized incidence ratio; TBI, total body irradiation.

[a] Including studies reporting SCC but no further characteristics of patients who developed SCC were described: Krishnan et al[15] (14 patients; sites not reported), Brown et al[18] (13 patients), Baker et al[7] (8 patients), Kolb et al[5] (4 patients), Bhatia et al[13] (3 patients), Friedrichs et al[21] (1 patient; site not reported).

[b] Fifty-three cutaneous SCC; however, SCC from noncutaneous sites included in further analysis and demographic information.

[c] Including studies reporting BCC but no other characteristics of patients who developed BCC were described: Brown et al[18] (26 patients), Krishnan et al[15] (13 patients), Baker et al[7] (11 patients), Kolb et al[5] (8 patients), Bhatia et al[13] (6 patients), Friedrichs et al[21] (3 patients).

[d] Including studies reporting melanoma but no further characteristics of patients who developed melanoma were described: Krishnan et al[15] (4 patients), Kolb et al[5] (2 patients).

[e] Excludes 5 patients with melanoma in situ.

Sex

Whereas males did not have an increased risk for BCC development in 2 studies, the risk of melanoma was increased in females in 1 study, and 2 studies showed conflicting data regarding increased risk of SCC in males. Rizzo et al[6] reported that males had a significantly increased risk of cutaneous SCC (RR, 11.9; $P < .05$) relative to females; however, females had an increased RR for melanoma (RR, 3.3; $P < .05$). In the Leisenring et al[4] study, sex was not associated with increased risk of BCC ($P = .53$) or any type of SCC ($P = .06$). Sex was also not a significant risk factor for BCC among patients who had not received total body irradiation (TBI) in the Schwartz et al[12] study ($P = .24$).

Race

Three studies suggested that race was a risk factor for skin cancer, particularly BCC. In the Krishnan et al[15] study, nonmelanoma skin cancer (NMSC) only developed in non-Hispanic whites, and race/ethnicity was a significant risk factor for malignant neoplasm development only when NMSCs were included in the multivariate Cox regression analysis (RR, 2.4 [95% CI, 1.2-4.6]; $P = .01$). In addition, Leisenring et al[4] reported a univariate hazard ratio (HR) of 4.5 for BCC for white patients relative to nonwhite patients. In the same study, race was not found to be a significant risk factor for SCC among the 86 white and 6 nonwhite patients who developed SCC.[4] A subsequent study by Schwartz et al,[12] adding to this cohort, reported an 8-fold higher risk for BCC for whites who had not undergone TBI relative to nonwhites who had not undergone TBI and no significant difference in risk among patients who had received TBI.

Age at Transplantation

Multiple studies showed that age at transplantation was a risk factor for skin cancer. One study showed that older age (≥55 years) at the time of transplantation was a significant risk factor for second primary neoplasms only when NMSC was included in the multivariate Cox regression analysis.[15] In contrast, Leisenring et al[4] reported that younger age at transplantation (<10 years) significantly increased the risk of both BCC and SCC, with all BCC occurring in patients who had undergone TBI at younger than 18 years. The Schwartz et al[12] study also showed an increased risk of BCC in TBI recipients younger than 40 years, particularly in children. Although the crude BCC incidence rate increased with age at HCT for non-TBI recipients, the overall risk of BCC did not vary with age at transplantation ($P = .06$).[12]

Conditioning Regimen

The studies did not report an increased risk of skin cancer associated with the type of conditioning medication used. Conditioning with TBI was associated with an increased risk of BCC and melanoma but not SCC.[4,6,12] Two studies reported the relative risk for BCC in patients who had received TBI to be 1.76 and 1.8 relative to patients who received non-TBI conditioning regimens.[4,12] The risk of BCC development did not vary significantly by the amount of radiation the patients received (7.5 to 18.4 Gy [to convert to rad, multiply by 100]).[12]

GVHD

In 3 of 4 studies, acute GVHD was not associated with an increased risk for BCC, SCC, or melanoma.[4,6,11,12] In contrast, 4 studies showed significant increased risk for BCC and SCC in patients who developed chronic GVHD,[4,6,11,12] and 1 study showed increased risk that was not statistically significant.[19]

Chronic GVHD was a significant risk factor for BCC development (HR, 1.5 [95% CI, 1.1-2.1]) in the Leisenring et al[4] study. Schwartz et al[12] also reported an increased risk of BCC in patients who had not undergone TBI who developed chronic GVHD (RR, 1.90 [95% CI, 1.22-2.96]; $P = .004$).

Chronic GVHD was associated with an increased risk of SCC in several studies.[4,6,11] Leisenring et al[4] found chronic GVHD to be a significant risk factor for mucosal and cutaneous SCC (HR, 2.8 [95% CI, 1.8-4.5]). Rizzo et al[6] also found a significantly increased risk of cutaneous SCC with chronic GVHD development (RR, 11.0; $P < .05$). The same study found that the risk of developing all types of SCC following chronic GVHD was significantly lower for patients with acute leukemia (RR, 2.16 [95% CI, 0.84-5.38]) relative to those with other primary diseases (RR, 9.51 [95% CI, 4.44-22.75]; $P = .02$ for interaction).[6] In the Curtis et al[11] study, there was a strong association between chronic GVHD and invasive cutaneous SCC relative to controls who developed other types of solid tumors (RR, 14.46). The same study showed that the risk of all types of SCC increased with increasing grade and duration of chronic GVHD.[11]

GVHD Treatment

The risk of SCC was significantly associated with the type and duration of immunosuppressive therapy.[11] Transplant recipients treated with immunosuppressants for 24 months or longer had an 8-fold higher risk for all types of SCC compared with those who were not treated for chronic GVHD.[11] That study showed the risk of all types of SCC to be increased by 18-fold in patients who received a combination of azathioprine, cyclosporine, and corticosteroids for GVHD relative to those not treated for chronic GVHD.[11] The risk of SCC associated with chronic GVHD therapy including azathioprine was strongest for cutaneous SCC relative to other SCC sites.[11] The risk for all types of SCC increased to greater than 50-fold among patients receiving other medications, including psoralen plus UV light, or limited-field TBI in addition to azathioprine, cyclosporine, and steroid therapy ($P < .001$).[11] There was only a nonsignificant 3-fold increase in risk for all types of SCC when patients received azathioprine and steroids without cyclosporine, and no increased risk for patients who received cyclosporine therapy without azathioprine, steroids alone, or other therapies not including azathioprine or cyclosporine.[11]

Discussion

Several risk factors for SCC, BCC, and melanoma in HCT recipients were identified in the 18 studies included in this review. Risk factors for SCC included a primary diagnosis of leukemia or severe aplastic anemia, younger age at transplantation, chronic GVHD, immunosuppression for greater than 24 months, and immunosuppressive regimens containing azathioprine. A primary diagnosis of leukemia, lymphoma, or malignant marrow disease was a risk factor for BCC. Additional risk factors for BCC included light skin color, younger age at transplantation, receipt of TBI, and chronic GVHD. Risk factors for melanoma included T-cell depletion, female sex, and receipt of TBI.

The underlying primary disease for which the HCT was required may be an important risk factor for subsequent skin cancer. It is well known that immunosuppressed individuals including those with chronic lymphocytic leukemia (CLL) have an increased risk of skin cancer development.[24] Cutaneous malignant neoplasms in patients with CLL show increased aggressiveness, resulting in a mortality rate as high from skin cancer as from CLL.[25] Therefore, we cannot completely separate the independent effects of the immunosuppression related to the primary disease on skin cancer development.

One of the main risk factors for melanoma and BCC is receipt of TBI. Radiation exposure, even with fractionated dosing intervals, causes irreparable damage to the basal layer.[4,12] Radiation exposure as a risk factor for BCC has been demonstrated among atomic bomb survivors, with the greatest risk among people who were young at the time of exposure.[26] The increased risk of developing BCC among younger cohorts may be due to greater radiation sensitivity.[12] Given that TBI increases the risk of cutaneous malignant neoplasm development, efforts to reduce radiation exposure, particularly in children and young adults, should continue.

Reduced-intensity or nonmyeloablative conditioning regimens have recently been introduced. The long-term effects of these regimens on tumorigenesis relative to myeloablative conditioning regimens have yet to be determined because second malignant neoplasms often take several years to develop after transplantation.[27]

Another major risk factor for skin cancer is chronic GVHD. Approximately 50% of HCT recipients will have some degree of chronic GVHD.[28] The risk increases with increased age and is higher among patients who receive transplants from female donors and among peripheral blood progenitor cell transplant (PBPCT) recipients relative to patients who undergo bone marrow transplantation.[5,21,29] Peripheral blood progenitor cell transplantation may be associated with lower rates of malignant relapse, and there has been a gradual trend toward the use of PBPCT over bone marrow transplantation.[29] This trend may portend an increased risk of SCC among transplant recipients.

The association between cutaneous malignant neoplasm development and chronic GVHD is poorly understood; however, cutaneous malignant neoplasms often develop at sites of previous chronic GVHD.[8] Inflammation and frequent cell division involved in GVHD could lead to the development of tetraploid and aneuploid keratinocytes, shortened telomeres, and haploinsufficiency of p53 that may account for subsequent SCC formation.[30] The differences in individual immune response and use of immunosuppressive therapy that may compromise immune surveillance may also play a role in cutaneous malignant neoplasm development.[4,5]

It is difficult to separate the effects of immunosuppression level from the severity of chronic GVHD. Patients with severe chronic GVHD were more likely to receive therapy with azathioprine, cyclosporine, and steroids over long periods of time.[11] In addition, the effect of type of immunosuppression on cutaneous malignant neoplasm risk is difficult to assess given changes in treatment regimens over time; furthermore, sufficient time may not have passed to assess the risk of newer treatment regimens. Agents such as tacrolimus and mycophenolate mofetil are now used more commonly than azathioprine for chronic GVHD treatment.

Several other factors that were not evaluated, such as a pretransplant history of skin cancer and voriconazole use, may be potential risk factors for skin cancer in HCT recipients. Voriconazole is a broad-spectrum antifungal approved by the Food and Drug Administration in 2002 that is used as treatment and prophylaxis for invasive fungal infections.[31] Voriconazole therapy is associated with photosensitivity, accelerated photoaging, SCC, and possibly melanoma, particularly among immunosuppressed patients.[32-35] Although the mechanism of voriconazole-associated photosensitivity is not fully understood, voriconazole may accelerate UV radiation–induced skin damage.[36] Cumulative dose and duration of voriconazole treatment may be independent risk factors for SCC development.[32,35,37] Additional studies need to be undertaken to determine the risk of voriconazole-associated malignant neoplasms in HCT recipients. Until this risk is fully understood, consideration of alternative antifungal therapies in HCT recipients who are at high risk for cutaneous malignant neoplasms and close skin surveillance in patients who require long-term voriconazole treatment may be warranted.

Pretransplant baseline screening and regular follow-up are important because the interval to diagnosis of cutaneous malignant neoplasms can be within several months of transplantation. Specifically, melanomas tend to occur within the first few years after transplantation. Long-term follow-up is also important because the risk of NMSC continues to increase 15 years after transplantation.[4] During the initial visit, a patient should have a baseline skin evaluation, education on how to perform self–skin examination, and an evaluation of individual cutaneous malignant neoplasm risk factors. **Table 3** shows an example questionnaire based on the included studies and developed by us that can help identify several potential risk factors. Given the fact that the data for this review are derived from multiple overlapping databases, the study is limited in

Table 3. Proposed Questionnaire That Could Help Identify Potential Skin Cancer Risk Factors in Hematopoietic Cell Transplant Recipients[a]

Questions	Risk	Source
1. Was the primary disease leukemia, lymphoma, or a malignant marrow disease?	BCC	Leisenring et al,[4] 2006
2. Was the primary disease leukemia or severe aplastic anemia?	SCC	Curtis et al,[11] 2005
3. Was the transplant T-cell depleted?	Melanoma	Rizzo et al,[6] 2009
4. Is the patient female?	Melanoma	Rizzo et al,[6] 2009
5. Is the patient white?	BCC	Krishnan et al,[15] 2013; Leisenring et al,[4] 2006; Schwartz et al,[12] 2009
6. Was the patient younger than 10 y at the time of transplantation?	BCC, SCC	Leisenring et al,[4] 2006; Schwartz et al,[12] 2009
7. Did the patient undergo total body irradiation?	BCC, melanoma	Leisenring et al,[4] 2006; Schwartz et al,[12] 2009; Rizzo et al,[6] 2009
8. Did the patient have chronic GVHD?	BCC, SCC	Leisenring et al,[4] 2006; Schwartz et al,[12] 2009; Rizzo et al,[6] 2009; Curtis et al,[11] 2005
9. Was the patient treated for longer than 24 mo with immunosuppressants?	SCC	Curtis et al,[11] 2005
10. Did the chronic GVHD treatment regimen include azathioprine?	SCC	Curtis et al,[11] 2005

Abbreviations: BCC, basal cell carcinoma; GVHD, graft-vs-host disease; SCC, squamous cell carcinoma.

[a] Questions address risk factors that were consistent among sources included.

its ability to conduct the multivariate analysis needed to truly identify the independent strength of each risk factor. In addition, further studies are needed to develop guidelines for screening intervals.

Hematologists, oncologists, primary care physicians, and dermatologists need to be aware of cutaneous malignant neoplasm risk factors in patients undergoing HCT. These specialties should work as a multidisciplinary team to coordinate patient care to ensure sufficient patient education, as well as adequate evaluation and treatment for subsequent malignant neoplasms.

There are several potential limitations to these studies. Unfortunately, many people die within a few years of transplantation. Therefore, the survival and mean follow-up for several of the studies may be too short to predict the actual incidence of skin cancer as survival times improve. In addition, several studies excluded NMSC from analysis because there is not a central reporting database for NMSC that would allow standardized incidence ratio and excess risk calculations. The actual risk for developing skin cancer in this population may also be difficult to determine given the changes in types of transplant and conditioning and treatment regimens.

Some studies likely contained patients who were exposed to local-field radiation and other carcinogenic therapies prior to transplantation. An adequate history of exposure and the effects of prior radiotherapy and medication use on the development of cutaneous malignant neoplasms could not be determined. In addition, skin cancers may have been underreported in the study populations, particularly in patients without complications.

Conclusions

Patients who undergo HCT are at an increased risk for skin cancers due to factors such as radiation exposure, chronic GVHD, and immunosuppression. Although the risk is less than that for SOTRs, patients need to be educated on the importance of self-examination and pursue regular follow-up with a dermatologist. Dermatologists should be part of the multidisciplinary team observing these patients and be aware of the risk factors that may increase this population's risk of cutaneous malignant neoplasms.

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Study concept and design: DePry, Caimi, Gerstenblith, Bordeaux.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: DePry, Vyas, Lazarus.
Critical revision of the manuscript for important intellectual content: All authors.
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