Risk factors for the development of cutaneous melanoma after allogeneic hematopoietic cell transplantation

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Background: Melanoma risk is increased after allogeneic hematopoietic cell transplantation (HCT), but specific risk factors are unknown.

Objective: Investigate risk factors for melanoma after allogeneic hematopoietic cell transplantation.

Methods: We conducted a nested case-control study of 140 melanoma cases and 557 controls (matched by age at HCT, sex, primary disease, survival time) through the Center for International Blood and Marrow Transplant Research.

Results: Melanoma risk was significantly increased among HCT survivors who received total body irradiation-based myeloablative conditioning (multivariable adjusted odds ratio [OR] = 1.77; 95% confidence interval [CI] = 1.00-3.15) or reduced-intensity conditioning containing melphalan (OR = 2.60; 95% CI = 1.13-6.02) or fludarabine (OR = 2.72; 95% CI = 1.02-7.30) versus busulfan-based myeloablative

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regimens; were diagnosed with acute graft-versus-host disease (GVHD) with stage 2+ skin involvement (OR = 1.92; 95% CI = 1.19-3.10), chronic GvHD without skin involvement (OR = 1.91; 95% CI = 1.03-3.57), or keratinocytic carcinoma (OR = 2.37; 95% CI = 1.16-4.83); and resided in areas with higher ambient ultraviolet radiation (ORtertile3 = 1.64; 95% CI = 1.01-2.67).

Limitations: Data on individual-level ultraviolet radiation exposure and clinical data on melanoma characteristics were lacking. Additionally, misclassification of melanoma is possible as not all pathology reports were available for review.

Conclusion: These results emphasize the importance of adherence to current surveillance guidelines (routine skin examination, photoprotection recommendations), particularly for HCT survivors at highest risk. (J Am Acad Dermatol 2020;83:762-72.)

Key words: allogeneic hematopoietic stem cell transplantation; ionizing radiation; late effects; melanoma; ultraviolet radiation.

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative treatment for a number of malignant and nonmalignant conditions, most frequently hematologic neoplasms. With improvements in clinical approaches, the number of allogeneic HCTs performed annually has increased substantially, and survival has improved, resulting in an expanding population of HCT survivors.[1,2] Unfortunately, survivors face increased risks for developing serious posttransplant complications, including new malignancies.[3-7] Among specific types of new malignancies, several studies have reported a 3- to 5-fold increased risk of melanoma after allogeneic HCT compared with the that of the general population.[4,8-10] Melanoma risk has been associated with receipt of total body irradiation (TBI)[4,10] and donor marrow T-cell depletion[4] but not graft-versus-host disease (GVHD),[11] although previous analyses were based on ≤15 melanoma cases.

Because of increased risks of melanoma and other skin cancers after HCT, long-term follow-up guidelines for HCT survivors include regular skin examination.[12] However, studies of screening behaviors suggest fewer than two-thirds of HCT survivors follow these recommendations.[13-15] We leveraged the detailed clinical data and large sample size of the Center for International Blood and Marrow Transplant Research (CIBMTR) database to comprehensively investigate melanoma risk factors after allogeneic HCT to identify high-risk patients who would likely benefit the most from adherence to screening guidelines and to contribute to the understanding of melanoma etiology.

CAPSULE SUMMARY

- This nested case-control study identifies novel risk factors for melanoma after allogeneic hematopoietic stem cell transplantation.
- The findings emphasize the importance of adherence to current surveillance guidelines (routine skin examination, photoprotection recommendations), particularly for transplant survivors at highest risk.

METHODS

Study population

We conducted a nested case-control study of melanoma among patients receiving a first allogeneic HCT between 1985 and 2012, as reported to the CIBMTR. Participating institutions are required to report data from all consecutive allogeneic HCT procedures, with compliance and data quality evaluated through electronic data checks, physician review of submitted records, and on-site audits. We excluded patients who (1) were from centers with <80% completeness of follow-up by 5 years after HCT; (2) did not provide informed consent; (3) were non-white or Hispanic (owing to the low risk of melanoma compared with whites[16]); (4) received a transplant from a syngeneic twin; (5) underwent transplantation for severe aplastic anemia, severe combined immunodeficiency syndrome, other immune disorders, or solid tumors (owing to differences in clinical approaches and treatments); or (6) were missing survival data. Among the remaining 21,590 individuals, we identified melanoma cases from standardized reporting forms at the time of transplant and at 100 days, 6 months, and annually after HCT or until death.

Initially eligible cases had a reported invasive or in situ melanoma diagnosis (N = 149; 75 [50%] confirmed by pathology report, 14 [9%] found not

to have melanoma and thus excluded, and 60 [40%] without available pathology reports) or a reported diagnosis of skin or other cancer subsequently confirmed by pathology report as melanoma (N = 11), resulting in a total of 146 potentially eligible cases. Four controls selected from the same population of potentially eligible patients were matched to each case based on age at HCT (±3 years), sex, primary disease, and survival time without developing melanoma (equal to or longer than the interval from HCT to development of melanoma for the matched case). Two cases were excluded because no matching controls could be found. Because only de-identified data were received, the study was exempt from ethics committee review at the National Cancer Institute.

Clinical data

CIBMTR data on patient and transplant characteristics were reviewed, considering all information before melanoma diagnosis (matched time point for controls) on patient demographics, primary disease, conditioning regimens, GVHD prophylaxis, occurrence of acute and/or chronic GVHD (including grade or extent of disease and skin involvement), GVHD treatment, and additional malignancies (Tables I to III). Individuals with a melanoma diagnosis before HCT were excluded from analyses (4 cases and their matched controls, plus 3 additional controls, leaving 140 melanoma cases and 557 matched controls). The site of melanoma occurrence, thickness, Clark level, and growth phase were recorded from pathology reports.

Individual-level data on ultraviolet radiation (UVR) exposure, an established melanoma risk factor,[17,18] were not available. We therefore approximated UVR exposure using satellite-based estimates of average noontime UVR[19] in the patient's geographic location at the time of HCT (for US patients: residential zip code when available, otherwise the state of the transplant center; for non-US patients: the latitude/longitude of the transplant center).[20] The resulting measure of radiation intensity (in milliwatts per square meter) was divided into tertiles based on the distribution in the total study population for analysis.

Statistical analysis

We used a multistage modeling approach to identify melanoma risk factors after allogeneic HCT, deriving odds ratios (ORs) and 95% confidence intervals (CIs) from conditional logistic regression models (SAS version 9.4; SAS Institute, Inc, Cary, NC). First, we estimated ORs separately for each patient- and transplant-related factor, adjusted for ambient UVR in tertiles. Then we constructed a final, multivariable-adjusted model, retaining all those patient- and transplant-related factors that were statistically significant at the traditional $P < .05$ cutoff value. Using this final model, we conducted exploratory analyses to investigate whether the identified melanoma risk factors were statistically significantly ($P < .05$) modified by age at allogeneic HCT or time from allogeneic HCT to development of melanoma (matched time point for controls) based on a likelihood ratio test.

RESULTS

Study population

Among 140 melanoma cases after allogeneic HCT, slightly more than half (56.7%) were male and the median age at transplant was 46 years (range, 1-73 years) (Table I). The most common indication for transplant was chronic myeloid leukemia (24.4%), followed by acute myeloid leukemia (17.9%) and acute lymphoblastic leukemia (17.9%). The distribution of first primary disease varied substantially by age at transplant (Supplemental Fig 1; available at DOI: 10.17632/x2t56y235g.1). Most patients received their transplants in the United States (cases, 84.3%; controls, 77.2%), and cases were more likely to have higher ambient UVR at transplant (tertile 3: cases, 40.7%; controls, 31.4%) (Table I).

Melanoma pathology

The median time from transplant to development of melanoma was 4 years (range, <1-24 years) (Supplemental Fig 2; available at DOI: 10.17632/x2t56y235g.1). Pathologically confirmed melanomas (N = 82) occurred most frequently on the limbs (36.6%) or trunk (36.6%) (Supplemental Table I; available at DOI: 10.17632/x2t56y235g.1). One-fifth (20.7%) of lesions were diagnosed in situ (Clark level I) and 43.9% were ≤1.0 mm thick, whereas 8.5% were ≥2.0 mm thick. In one-fifth (20.7%) of cases, the melanoma had spread into the reticular or deep dermis (Clark level IV).

Melanoma risk factors

Nearly all cases and controls received a peripheral blood or bone marrow graft, most commonly from an unrelated donor (cases, 65.0%; controls. 54.6%) (Table II). Nearly half of patients (cases, 46.4%; controls. 42.5%) received a TBI-based myeloablative conditioning regimen, whereas about one-third of patients (cases, 33.6%; controls, 30.2%) received a reduced-intensity conditioning regimen. Among

Table I. Selected patient and transplant characteristics of melanoma cases and matched controls, Center for International Blood and Marrow Transplant Research program, 1985-2012

	Melanoma cases (n = 140)		Matched controls (n = 557)	
Characteristic	**n**	**%**	**n**	**%**
Age at transplant, years*				
<40	54	38.6	214	38.4
40-<55	48	34.3	190	34.1
≥55	38	27.1	153	27.5
Sex*				
Male	79	56.4	316	56.7
Female	61	43.6	241	43.3
Indication for transplant*				
Acute lymphocytic leukemia	25	17.9	100	18.0
Acute myeloid leukemia	25	17.9	100	18.0
Myeloproliferative disorder	13	9.3	52	9.3
Other acute leukemia	1	0.7	4	0.7
Chronic myeloid leukemia	34	24.3	136	24.4
Chronic myelomonocytic leukemia	2	1.4	8	1.4
Myeloproliferative neoplasm	9	6.4	36	6.5
Chronic lymphocytic leukemia	12	8.6	48	8.6
Non-Hodgkin lymphoma	17	12.1	65	11.7
Hodgkin lymphoma	1	0.7	4	0.7
Multiple myeloma	1	0.7	4	0.7
Region†				
United States	118	84.3	430	77.2
Europe	15	10.7	88	15.8
Canada	3	2.1	20	3.6
Australia/New Zealand	4	2.9	19	3.4
Ambient ultraviolet radiation†				
Tertile 1	42	30.0	197	35.4
Tertile 2	41	29.3	185	33.2
Tertile 3	57	40.7	175	31.4
Karnofsky score before preparative regimen				
≥90	108	77.1	410	73.6
<90	29	20.7	114	20.5
Missing	3	2.1	33	5.9
Transplant year				
1985-1998	37	26.4	203	36.4
1999-2005	57	40.7	173	31.1
2006-2012	46	32.9	181	32.5
Donor age, median (range), years	36 (5-70)		36 (<1-73)	
Time from transplant to melanoma/study inclusion,* median (range), years	4 (<1-24)		4 (<1-24)	

*Four controls were matched to each case by age (±3 years), sex, first primary disease, and survival time without developing melanoma at least as long as the matched case's interval from transplant to developing melanoma.
†Ambient ultraviolet radiation was based on the region of patient residence, measured as radiation intensity (milliwatt per square meter) and divided into tertiles. If the zip code was not available, the nearest transplant center was used. Tertile 1: <23.0 mW/m^2; tertile 2: 23.0-<31.6 mW/m^2; tertile 3: ≥31.6 mW/m^2.

patient and transplant characteristics, models adjusted only for ambient UVR identified donor group, conditioning regimens, and donor/recipient cytomegalovirus serostatus as potential melanoma risk factors. Receipt of a T-cell–depleted transplant was not associated with melanoma risk (cases, 26.4%; controls, 33.6%; OR, 0.72; 95% CI, 0.47-1.11). Among posttransplant characteristics, models adjusted only for ambient UVR identified acute and chronic GVHD and keratinocytic carcinoma as potential risk factors (Table III). Two-thirds (67.9%) of cases and 59.8% of controls were diagnosed with acute GVHD, and median time from acute GVHD with stage 2+ skin involvement to melanoma diagnosis for cases was

Table II. Risk for melanoma after allogeneic hematopoietic cell transplantation according to patient and transplant characteristics, adjusted for ambient ultraviolent radiation only*

Patient and transplant characteristics	Cases (n = 140)		Controls (n = 557)		OR*	95%CI	*P* value	Overall *P* value†
	n	%	n	%				
Donor group								
HLA-identical sibling	40	28.6	221	39.7	Ref			**.05**
Unrelated	91	65.0	304	54.6	**1.68**	**1.10-2.57**	**.02**	
Other related, cord blood	9	6.4	32	5.7	1.71	0.74-3.98	.21	
Graft source								
Bone marrow	66	47.1	294	52.8	Ref			.28
Peripheral blood	68	48.6	244	43.8	1.44	0.89-2.33	.13	
Cord blood	6	4.3	19	3.4	1.64	0.60-4.48	.34	
Conditioning‡								
MA − TBI	28	20.0	152	27.3	Ref			.16
MA + TBI	65	46.4	237	42.5	1.61	0.94-2.78	.09	
RIC + TBI	10	7.1	49	8.8	1.40	0.57-3.44	.46	
RIC − TBI	37	26.4	119	21.4	1.88	0.98-3.62	.06	
Conditioning regimen								
MA: Busulfan ± others	27	19.3	146	26.2	Ref			.47
MA: TBI ± others	65	46.4	237	42.5	1.61	0.93-2.80	.09	
MA: Other	1	0.7	6	1.1	0.93	0.11-8.09	.95	
RIC: TBI ± others	10	7.1	49	8.8	1.38	0.55-3.44	.49	
RIC: Busulfan ± others	9	6.4	39	7.0	1.48	0.58-3.74	.41	
RIC: Melphalan ± others	14	10.0	36	6.5	2.14	0.95-4.78	.07	
RIC: Fludarabine ± others	10	7.1	26	4.7	2.38	0.90-6.24	.08	
RIC: Other	4	2.9	18	3.2	1.39	0.41-4.69	.60	
Antithymocyte globulin in conditioning regimen or GVHD prophylaxis								
No	113	80.7	429	77.0	Ref			.34
Yes	27	19.3	128	23.0	0.79	0.48-1.30	.35	
Alemtuzumab in conditioning regimen or GVHD prophylaxis								
No	136	97.1	540	96.9	Ref			.66
Yes	4	2.9	17	3.1	0.79	0.26-2.40	.67	
GVHD prophylaxis								
TAC/CSA + MTX ± other(s)	90	64.3	329	59.1	Ref			.08
T-cell depletion (ex vivo or CD34 selection)	11	7.9	69	12.4	0.63	0.32-1.25	.19	
TAC/CSA + MMF ± other(s)	27	19.3	81	14.5	1.35	0.78-2.32	.28	
TAC/CSA ± other(s)	11	7.9	61	11.0	0.65	0.32-1.29	.22	
Other§	1	0.7	17	3.1	0.23	0.03-1.77	.16	
Pretransplant T-cell depletion¶								
No	103	73.6	370	66.4	Ref			.13
Yes	37	26.4	187	33.6	0.72	0.47-1.11	.14	
Donor/recipient CMV serostatus								
Negative/negative	61	43.6	198	35.5	Ref			.32
Negative/positive	32	22.9	134	24.1	0.74	0.46-1.21	.23	
Positive/negative	15	10.7	57	10.2	0.83	0.44-1.57	.58	
Positive/positive	25	17.9	129	23.2	0.61	0.36-1.03	.06	
Unknown	7	5.0	39	7.0	0.57	0.24-1.32	.19	
Donor/recipient sex								
Male/male	48	34.3	172	30.9	Ref			.11
Male/female	36	25.7	101	18.1	2.41	0.69-8.39	.17	
Female/male	17	12.1	93	16.7	0.67	0.36-1.24	.20	

Continued

Table II. Cont'd

Patient and transplant characteristics	Cases (n = 140) n	Cases (n = 140) %	Controls (n = 557) n	Controls (n = 557) %	OR*	95%CI	*P* value	Overall *P* value†
Female/female	20	14.3	104	18.7	1.37	0.38-4.99	.63	
Unknown/male or female	19	13.6	87	15.6	0.92	0.43-1.95	.82	

Bold text indicates significance at the $P < .05$ level.

CI, Confidence interval; *CMV*, cytomegalovirus; *CSA*, cyclosporine; *GVHD*, graft-versus-host disease; *HLA*, human leukocyte antigen; *MA*, myeloablative; *MMF*, mycophenolate mofetil; *MTX*, methotrexate; *OR*, odds ratio; *Ref*, referent; *RIC*, reduced-intensity conditioning; *TAC*, tacrolimus; *TBI*, total body irradiation.

*Models were adjusted for ambient ultraviolet radiation in tertiles (see Table I footnote). Tertile 1: referent; tertile 2: OR, 1.04; 95% CI, 0.64-1.67; tertile 3: OR, 1.53; 95% CI, 0.97-2.34.

†The likelihood ratio statistic was calculated comparing model fit for a model with ambient UVR alone with a model also including the variable of interest.

‡MA + TBI most frequently included TBI + cyclophosphamide (cases = 50, controls = 177). RIC + TBI most frequently included TBI + fludarabine (cases = 8, controls = 30).

§Other GVHD prophylaxis included posttransplant cyclophosphamide and 3 controls with missing data.

¶Pretransplant T-cell depletion included T-cell depletion during conditioning or GVHD prophylaxis, including ex vivo T-cell depletion, CD34 selection, antithymocyte globulin, and alemtuzumab.

4.7 years (range, 0.4-23.9) and to selection for controls was 4.4 years (range, 0.1-23.9). Additionally, limited/extensive chronic GVHD developed in 65.7% of cases and 63.7% of controls; the median time from chronic GVHD without skin involvement to development of melanoma for cases was 2.4 years (range, 0.5-15.5) and from chronic GVHD to selection for controls was 3.6 years (range, 0.1-20.6). Most patients with acute or chronic GVHD received steroid treatment and more than one line of additional immunosuppressive therapy. Relapse and subsequent infusions occurred in a minority of patients and were not associated with melanoma risk. After transplant but before melanoma diagnosis (matched time point for controls), 12.9% of melanoma cases were diagnosed with a keratinocytic carcinoma (basal or squamous cell carcinoma) and 4.3% with another nonskin neoplasm, compared with 6.1% and 3.2%, respectively, of controls. Median time from keratinocytic carcinoma to melanoma diagnosis for cases was 3.5 years (range, 0.4-12.0 years) and to selection for controls was 2.8 years (range, 0.5-15.9 years).

We constructed a final multivariable model, including all patient-, transplant-, and posttransplant-related factors that were significantly associated with melanoma risk. In this final model (Table IV), melanoma risk remained significantly increased for allogeneic HCT recipients who met the following conditions:

1. Residence in a geographic area at the time of transplant with higher ambient UVR (tertile 3 versus 1: OR, 1.64; 95% CI, 1.01-2.67).
2. Receipt of TBI-based myeloablative conditioning (OR, 1.77; 95% CI, 1.00-3.15) or reduced-intensity conditioning with melphalan (OR, 2.60; 95% CI, 1.13-6.02) or fludarabine (OR, 2.72; 95% CI, 1.02-7.30) compared with those receiving busulfan-based myeloablative conditioning.
3. Development of acute GVHD with stage 2+ skin involvement (maculopapular rash ≥25% of body surface or generalized erythroderma; OR, 1.92; 95% CI, 1.19-3.10) versus no acute GVHD.
4. Development of chronic GVHD without skin involvement (OR, 1.91; 95% CI, 1.03-3.57) versus no chronic GVHD.
5. Development of keratinocytic carcinoma (OR, 2.37; 95% CI, 1.16-4.83).

After accounting for these variables, donor type, type of GVHD prophylaxis, and donor/recipient cytomegalovirus status were no longer significantly associated with melanoma risk.

Exploratory analyses stratifying the multivariable-adjusted risk estimates for melanoma by age at transplant (Supplemental Table II; available at DOI: 10.17632/x2t56y235g.1) or time from transplant to melanoma (matched interval for controls; Supplemental Table III; available at DOI: 10.17632/x2t56y235g.1) revealed no statistically significant heterogeneity, except that the risk of melanoma associated with ambient UVR was more pronounced for melanomas occurring ≥6 years after transplant (tertile 3 vs 1: OR, 3.04; 95% CI, 1.22-7.56; $P_{heterogeneity}$ by latency = .014). In contrast, ambient UVR was not associated with melanomas occurring earlier (<3 years: OR, 1.37; 95% CI, 0.62-3.04; 3 to <6 years: OR, 0.98; 95% CI, 0.36-2.71). Sensitivity

Table III. Risk for melanoma after allogeneic hematopoietic cell transplantation according to posttransplant characteristics, adjusted for ambient ultraviolet radiation only*

	Cases (n = 140)		Controls (n = 557)					
Posttransplant characteristics	n	%	n	%	OR*	95% CI	*P* value	Overall *P* value†
Acute GVHD grade								
No acute GVHD	45	32.1	224	40.2	Ref			.20
Acute GVHD grade 1	28	20.0	115	20.6	1.24	0.74-2.09	.42	
Acute GVHD grade 2+	62	44.3	204	36.6	**1.56**	**1.00-2.43**	**.05**	
Missing	5	3.6	14	2.5	2.03	0.64-6.42	.23	
Acute GVHD skin involvement‡								
No acute GVHD	45	32.1	224	40.2	Ref			.09
No/unknown skin involvement	9	6.4	29	5.2	1.45	0.62-3.38	.39	
Stage 0/1	25	17.9	120	21.5	1.08	0.62-1.87	.79	
Stage 2+	61	43.6	184	33.0	**1.69**	**1.08-2.63**	**.02**	
Steroid treatment for acute GVHD								
No acute GVHD	45	32.1	224	40.2	Ref			.30
Did not receive treatment	3	2.1	11	2.0	1.51	0.40-5.74	.55	
Received steroids	88	62.9	304	54.6	1.48	0.98-2.24	.06	
Received treatment other than steroids	4	2.9	18	3.2	1.14	0.37-3.56	.82	
Number of lines of therapy for acute GVHD								
No acute GVHD	45	32.1	224	40.2	Ref			.29
No therapy	3	2.1	12	2.2	1.39	0.37-5.21	.63	
1 line of therapy	11	7.9	45	8.1	1.23	0.58-2.62	.59	
>1 line of therapy	81	57.9	276	49.6	1.50	0.99-2.28	.06	
Chronic GVHD								
No chronic GVHD	48	34.3	202	36.3	Ref			.62
Limited/extensive	92	65.7	355	63.7	1.11	0.73-1.69	.62	
Chronic GVHD skin involvement								
No chronic GVHD	48	34.3	202	36.3	Ref			.13
Missing skin involvement	2	1.4	6	1.1	1.37	0.27-6.96	.70	
No skin involvement	24	17.1	57	10.2	**1.86**	**1.03-3.36**	**.04**	
Yes skin involvement	66	47.1	292	52.4	0.96	0.62-1.50	.86	
Steroid treatment for chronic GVHD								
No chronic GVHD	48	34.3	202	36.3	Ref			.46
Did not receive treatment	5	3.6	11	2.0	1.94	0.64-5.85	.24	
Received steroids	83	59.3	317	56.9	1.14	0.74-1.75	.56	
Received treatment other than steroids	4	2.9	27	4.8	0.62	0.21-1.87	.40	
Number of lines of therapy for chronic GVHD								
No chronic GVHD	48	34.3	202	36.3	Ref			.51
No therapy	5	3.6	12	2.2	1.79	0.60-5.29	.30	
1 line of therapy	13	9.3	38	6.8	1.55	0.76-3.19	.23	
>1 line of therapy	74	52.9	305	54.8	1.03	0.66-1.59	.91	
Relapse								
No§	121	86.4	459	82.4	Ref			.22
Yes	19	13.6	98	17.6	0.71	0.41-1.24	.23	
Infusion								
No	126	90.0	500	89.8	Ref			.87
Yes	14	10.0	57	10.2	0.95	0.51-1.78	0.88	
Keratinocytic carcinoma								
No	122	87.1	524	94.1	Ref			**.01**
Yes	18	12.9	33	5.9	**2.54**	**1.28-5.06**	**.01**	

Continued

Table III. Cont'd

Posttransplant characteristics	Cases (n = 140) n	Cases (n = 140) %	Controls (n = 557) n	Controls (n = 557) %	OR*	95% CI	*P* value	Overall *P* value†
Other neoplasm (non-skin)¶								
No	134	95.7	538	96.6	Ref			.53
Yes	6	4.3	19	3.4	1.37	0.52-3.61	.52	

Bold text indicates significance at the $P < .05$ level.

CI, Confidence interval; *GVHD*, graft-versus-host disease; *OR*, odds ratio; *Ref*, referent.

*Models were adjusted for ambient ultraviolet radiation in tertiles (see Table I footnote). Tertile 1: referent; tertile 2: OR, 1.04; 95% CI, 0.64-1.67; tertile 3: OR, 1.53; 95% CI, 0.97-2.34.

†The likelihood ratio statistic was calculated comparing model fit for a model with ambient ultraviolet radiation alone with a model also including the variable of interest.

‡Acute GVHD skin involvement: stage 0 or 1 includes no rash or maculopapular rash <25% of body surface; stage 2+ includes maculopapular rash ≥25% of body surface or generalized erythroderma.

§No relapse includes one control with missing data.

¶Nonskin neoplasm diagnoses included breast cancer (2 controls); genitourinary malignancy (3 cases, 4 controls); gastrointestinal malignancy (1 case, 1 control); thyroid cancer (1 case, 1 control); spindle cell carcinoma (1 control); myelodysplastic syndrome (1 control); lymphoma (1 case, 1 control); T-cell large granular lymphocytic leukemia (1 control); and unknown (7 controls).

analyses yielded generally similar results when excluding non-US patients, those who had another cancer after transplant but before their diagnosis of melanoma (or matched time point for controls), or case sets for which the melanoma was not confirmed by pathology report or was diagnosed in situ.

DISCUSSION

Using large-scale, detailed clinical data, we show that the increased risk of melanoma after allogeneic HCT has a multifactorial etiology, with contributions from patient, transplant, and posttransplant risk factors. Specifically, melanoma risk was increased among recipients who received particular conditioning regimens, were diagnosed with certain types of GVHD or keratinocyte carcinoma, and resided in areas with higher ambient UVR. Although one-fifth of melanomas were diagnosed in situ, more than half were >1 mm thick at diagnosis, and 8.5% were ≥2 mm thick, emphasizing the importance of awareness of increased melanoma risk in allogeneic HCT recipients. Our results provide insight into melanomagenesis and support prioritization of high-risk survivors for adherence to prevention and screening recommendations.

We observed increased melanoma risk after TBI-based myeloablative conditioning regimens and after reduced-intensity conditioning regimens containing either melphalan or fludarabine compared with busulfan-based myeloablative conditioning. Although melanoma has not been associated with ionizing radiation exposure in most previous settings,[21] our results support the intriguing possibility that ionizing radiation could be a risk factor for melanoma among immunosuppressed individuals. An interplay between cytotoxic agents and immune mechanisms also is consistent with our observation of increased risk of melanoma after melphalan- and fludarabine-based reduced-intensity conditioning regimens. This hypothesis has been proposed previously to explain the increased melanoma risk among survivors of Hodgkin lymphoma, who have long-term immune dysfunction after cytotoxic therapy,[22] as well as survivors of chronic lymphocytic leukemia/small lymphocytic lymphoma, particularly those receiving fludarabine.[23] Additionally, melphalan has recently been shown to have a range of immunomodulatory effects.[24] However, comparison of results from other cancer survivors with allogeneic HCT recipients requires caution because of lower doses and short duration of use of specific agents during HCT conditioning versus primary cancer treatment, although some patients may have had more comparable exposures during pre-HCT therapy.

Our observation of increased melanoma risk associated with certain types of GVHD also supports the importance of immunosuppression in melanoma development after HCT and contrasts previous reports of graft-antitumor responses against cutaneous squamous cell carcinoma and nevi.[25,26] Our large sample size enabled separation of acute and chronic GVHD according to skin involvement, with further stratification of acute GVHD skin involvement by stage. Whereas mature donor T cells are thought to play a key role in acute GVHD, the immune dysregulation underlying chronic GVHD is more complex.[27,28] Limitations of the available GVHD data—particularly the lack of information on GVHD duration and treatment—which could

Table IV. Final multivariable model identifying risk factors for melanoma after allogeneic hematopoietic cell transplantation

Characteristics*	Cases	Controls	OR	95% CI	Overall *P* value†
Ambient ultraviolet radiation					
Tertile 1	30	147	Ref		.10
Tertile 2	27	143	1.12	0.67-1.87	
Tertile 3	44	133	**1.64**	**1.01-2.67**	
Conditioning regimen					
MA: Busulfan ± others	27	146	Ref		.26
MA: TBI ± others	65	237	**1.77**	**1.00-3.15**	
MA: Other	1	6	0.71	0.07-6.91	
RIC: TBI ± others	10	49	1.75	0.69-4.47	
RIC: Busulfan ± others	9	39	1.82	0.70-4.76	
RIC: Melphalan ± others	14	36	**2.60**	**1.13-6.02**	
RIC: Fludarabine ± others	10	26	**2.72**	**1.02-7.30**	
RIC: Other	4	18	1.68	0.49-5.76	
Acute GVHD skin involvement‡					
No acute GVHD	45	224	Ref		**.04**
No/unknown skin involvement	9	29	1.36	0.56-3.32	
Stage 0/1	25	120	1.14	0.64-2.02	
Stage 2+	61	184	**1.92**	**1.19-3.10**	
Chronic GVHD skin involvement					
No chronic GVHD	48	202	Ref		**.03**
Missing skin involvement	2	6	1.56	0.30-8.20	
No skin involvement	24	57	**1.91**	**1.03-3.57**	
Yes skin involvement	66	292	0.81	0.50-1.29	
Keratinocytic carcinoma					
No	122	524	Ref		**.02**
Yes	18	33	**2.37**	**1.16-4.83**	

Bold text indicates significance at the $P < .05$ level.

CI, Confidence interval; *GVHD*, graft-versus-host disease; *MA*, myeloablative; *OR*, odds ratio; *Ref*, referent; *RIC*, reduced-intensity conditioning; *TBI*, total body irradiation.

*Patient, transplant, and posttransplant characteristics were included in the final multivariable model if $P < .05$ for any specific category or the overall $P < .05$.

†The likelihood ratio statistic was calculated comparing the full model with a model without the variable of interest.

‡Acute GVHD skin involvement: stage 0 or 1 includes no rash or maculopapular rash <25% of body surface; stage 2+ includes maculopapular rash ≥25% of body surface or generalized erythroderma.

contribute to melanoma risk, highlight the importance of detailed clinical information for investigation of risk factors for subsequent neoplasms after allogeneic HCT. Future studies aimed toward better understanding of a potential immunologic contribution to melanomagenesis should directly measure immune function, including T-cell numbers, functional capacities, and diversity, and include other immunosuppressed individuals, such as solid organ transplant recipients and individuals with HIV/AIDS, who also have an increased risk of melanoma.[29]

Keratinocytic carcinoma after allogeneic HCT was associated with a >2-fold increased melanoma risk. Keratinocytic carcinomas primarily have been linked to UVR exposure and phenotypic characteristics in the general population[30,31] (in which the relationship between keratinocytic carcinomas and melanoma is well established[32]), immunosuppression and the antifungal agent voriconazole after transplantation,[33-36] and ionizing radiation exposure after childhood cancer.[37] Keratinocytic carcinomas in the setting of allogeneic HCT appear to have a multifactorial etiology with contributions from each of these factors.[38] Our findings are consistent with a reported association between keratinocytic carcinoma and melanoma after solid organ transplantation.[39] Heightened vigilance after keratinocytic carcinoma is unlikely to fully explain the association we observed because of the time lag between keratinocytic carcinoma and melanoma. Shared etiologic factors likely play a role, and the

occurrence of a keratinocytic carcinoma may be clinically useful for identifying patients who may be at elevated risk for development of melanoma.

The modestly increased risk of melanoma that we observed among allogeneic HCT recipients residing in geographic areas with higher ambient UVR is consistent with previous literature reports for the general population.[17,18] The association with UVR for melanomas occurring ≥6 years after transplant could reflect a synergistic effect of UVR exposure and immunosuppression. Although the ability to adjust for ambient UVR is a strength of our study, we were unable to completely investigate the potential confounding or modification of transplant-related melanoma risk factors by UVR exposure because we lacked detailed, individual-level data (eg, lifetime residential history, recreational sun exposure, indoor tanning, sunburn history, phenotypic characteristics, sun protection behaviors). We also lacked data on the number and type of nevi. Future studies of melanoma after transplantation should seek to collect such data from HCT recipients to better quantify UVR exposure for potential risk stratification of screening guidelines.

In addition to the lack of detailed data on immune function and UVR exposure noted earlier, several additional limitations should be accounted for in our analysis. Misclassification of melanoma may have occurred because pathology reports were available for only 82 (59%) cases. Additionally, some melanoma cases may not have been reported by transplant centers, although we minimized selection bias by restricting eligible patients to those from transplant centers with at least 80% completeness of follow-up by 5 years after HCT. Further detailed clinical data on the melanoma cases (eg, ulceration) were not available, nor was information on other potential risk factors such as voriconazole use. Increased surveillance in certain subsets of patients could explain some of our results, although the time lag between certain risk factors (eg, acute GVHD with stage 2+ skin involvement, diagnosis of keratinocytic carcinoma) and melanoma development argues against surveillance as the only explanation for our observations. With evolving HCT clinical practices, future studies should investigate whether current approaches (eg, increased use of cord blood, changes in conditioning regimens) are associated with melanoma risk.

CONCLUSION

We report novel associations between melanoma risk and specific conditioning regimens, occurrence of acute and chronic GVHD, and occurrence of keratinocyte carcinoma, suggesting a multifactorial etiology for melanoma after allogeneic HCT. Our results emphasize the importance of adherence to current surveillance guidelines for HCT recipients, specifically routine skin examination, heightened skin cancer awareness, and long-term photoprotection recommendations, particularly for those survivors at highest risk. Further research on melanoma screening cost-effectiveness is warranted.

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