Morbidity and Mortality Differences Between Hematopoietic Cell Transplantation Survivors and Other Cancer Survivors

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ABSTRACT

Purpose

To compare the risks of serious health outcomes among hematopoietic cell transplantation (HCT) survivors versus a matched population of patients with cancer who did not undergo HCT, where the primary difference may be exposure to HCT.

Methods

Two-year HCT survivors treated at a comprehensive cancer center from 1992 through 2009 who were Washington State residents ($n = 1,792$; 52% allogeneic and 90% hematologic malignancies) were frequency matched by demographic characteristics and underlying cancer diagnosis (as applicable) to non-HCT 2-year cancer survivors, using the state cancer registry ($n = 5,455$) and the general population ($n = 16,340$) using driver's license files. Late outcomes for all three cohorts were ascertained from the state hospital discharge and death registries; subsequent cancers were ascertained from the state cancer registry.

Results

After median follow-up of 7.1 years, HCT survivors experienced significantly greater rates of hospitalization compared with matched non-HCT cancer survivors (280 v 173 episodes per 1,000 person-years, $P < .001$) and greater all-cause mortality (hazard ratio [HR], 1.1; 95% CI, 1.01 to 1.3). HCT survivors had more hospitalizations or death with infections (10-year cumulative incidence, 31% v 22%; HR, 1.4; 95% CI, 1.3 to 1.6) and respiratory complications (cumulative incidence, 27% v 20%; HR, 1.4; 95% CI, 1.2 to 1.5). Risks of digestive, skin, and musculoskeletal complications also were greater among HCT versus non-HCT cancer survivors. The two groups had similar risks of circulatory complications and second cancers. Both HCT and non-HCT cancer survivors had significantly greater 10-year cumulative incidences of all major organ-system outcomes versus the general population.

Conclusion

History of HCT was associated with late morbidity and mortality among cancer survivors. In particular, clinicians who care for HCT survivors should be aware of their high rates of late respiratory and infectious complications.

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INTRODUCTION

The use of autologous and allogeneic hematopoietic cell transplantation (HCT) to treat high-risk malignancies has increased markedly during the past 25 years.¹ Among ≥ 2 -year HCT survivors, more than 70% remain long-term survivors, and nearly 250,000 HCT survivors (estimated 60% autologous; 40% allogeneic) are predicted to be living in the United States by the year 2020.² Thus, it becomes important to clarify the patterns of late morbidity and mortality in this population.^{3,4} Most studies of late serious health outcomes

following HCT have focused on original disease relapse, chronic graft versus host disease (GVHD), and second cancers. The incidence of other serious outcomes among HCT survivors remains less well described, although rates of serious cardiopulmonary disease, long-term infectious complications, and overall rates of serious chronic conditions also are greater than in the general population.⁵⁻¹⁰ Many previous studies were limited by small sample size, potential response or survival biases, or loss to follow-up when they depended on patient self-report and data from transplant centers.

ASSOCIATED CONTENT

Data Supplement

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Furthermore, it is unclear whether HCT survivors are at greater risk of adverse long-term health conditions compared with other cancer survivors.

To address these limitations, we linked a large HCT cohort with state hospital and death registry data and compared the burden of hospitalizations and deaths among ≥ 2 -year HCT survivors with those experienced by both the general population and a non-HCT cancer survivor cohort derived from the state cancer registry and matched on the same underlying diagnoses. These data provided population-based estimates of the absolute and relative risks of serious health outcomes affecting each group and allowed us to examine whether HCT survivors have risks beyond those experienced by cancer survivors who did not receive HCT.

METHODS

HCT Survivor and Comparison Cohorts

HCT survivors were Washington State residents treated at the Fred Hutchinson Cancer Research Center (FHCRC), a National Cancer Institute-designated comprehensive cancer center and the only accredited institution that performs allogeneic HCT in Washington (a few other institutions perform autologous HCT only). The Fred Hutchinson Cancer Research Center (FHCRC) database was screened to identify patients who received any HCT from 1992 through 2009 ($n = 7,108$), were alive ≥ 2 years post-transplant ($n = 4,081$), were state residents at the time of transplantation ($n = 1,929$), and received transplantation for a malignant condition ($n = 1,792$). Race and ethnicity, clinically recorded pretransplant diagnosis, and transplant-related exposures (eg, donor type, stem-cell source, conditioning regimen, chronic GVHD requiring systemic immunosuppressive treatment) were obtained from the FHCRC database.

A comparison cohort of patients with cancer diagnoses was identified from the Washington State Cancer Registry (non-HCT group). After excluding subjects who were FHCRC HCT survivors, the remaining state residents who had an initial cancer diagnosis from 1992 through 2009 and survived ≥ 2 years were randomly selected and frequency matched to HCT survivors at a 3:1 ratio by sex, age at cancer diagnosis or HCT (10-year age increments plus age < 20 years and ≥ 60 years), year of cancer diagnosis or HCT (2-year increments), and cancer diagnosis group ($n = 5,455$; Data Supplement).

A separate, population-based noncancer comparison cohort was available from the Washington State Department of Licensing (DOL) files for 1992 through 2009 that did not overlap with either the HCT or non-HCT groups. Subjects had been randomly selected from these files to be frequency matched (10:1 ratio; $n = 16,340$) based on their age at and year of driver's license issuance or renewal to ≥ 2 -year FHCRC HCT survivors who were state residents and ≥ 16 years of age at HCT, by sex, age at year of HCT ($n = 1,634$; including 68 HCT survivors who had received transplantation for nonmalignant diseases). State death records were screened to ensure that the comparison subjects did not die within 2 years of licensing.

Outcomes Ascertainment

For hospitalization data, we used the Washington State Comprehensive Hospital Abstract Reporting System, a database of all hospital discharges from non-federal facilities. This database contains up to nine diagnosis codes (International Classification of Diseases, 9th revision [ICD]) for each hospitalization during the years of study. Identifiers allowed longitudinal tracking of individuals across multiple hospitalizations and linkage to outside data sources. For mortality, we used the state death registry, which recorded the primary and up to six contributing causes of death (ICD-10) and includes deaths of residents who died in

neighboring states. Similar to our previous work, we used a sequential deterministic linkage strategy to link survivors and comparison subjects to hospital discharge and death records from 1992 through 2011.^{11,12} Variables available for linkage included components of names, birth date, sex, zip code, county of residence, date of HCT and corresponding hospitalization, and date of death (if applicable).

We assigned linked ICD-9 and equivalent ICD-10 codes to major outcome categories, primarily based on organ systems (Data Supplement), occurring ≥ 2 years after the index date (ie, transplant for HCT group, cancer diagnosis for non-HCT group, and drivers' licensing date for DOL group). For each category, we also examined infection- and noninfection-associated codes separately. To ascertain subsequent cancers, the state cancer registry was used to identify new cancers occurring among HCT and non-HCT cancer survivors.

Statistical Analysis

For each outcome, we estimated the 10-year cumulative incidence and associated differences among HCT and comparison cohorts starting 2 years from the index date. Follow-up of individuals without events was censored on December 31, 2011 or earlier if they died of any cause other than the specific outcome category examined.¹³ Analysis of pregnancy outcomes was restricted to women 15 to 44 years of age during the study period. Mental health outcomes were available only for individuals ≥ 18 years of age because of state policy.

We used Cox proportional hazards models with age as the time scale, left-truncated with individuals entering the analysis 2 years from their index date, to estimate the hazard ratios (HRs) and 95% CIs for each outcome adjusted for sex, year of index event, and underlying diagnosis group for HCT versus non-HCT cancer survivors.¹⁴ In analyses restricted to HCT recipients, using a time since transplant scale, we also examined the contributions of race and ethnicity, age at transplantation, donor type, chronic GVHD, and relapse of the original disease within the first 2 years after HCT. Subanalyses examined these relationships among ≥ 5 -year survivors. History of total body irradiation (TBI; none, < 10 Gy, and ≥ 10 Gy) was examined but was not included in final models because we did not have information regarding radiotherapy received before referral for HCT. Global tests of proportionality based on Schoenfeld residuals were used to ensure that proportional hazards assumptions were met ($P \geq .05$); covariates with nonproportional hazards were treated as time-varying.¹⁴ Finally, given that the burden of some outcomes may be better described by a model that allows multiple events rather than time-to-first event, we also applied Poisson regression to estimate the relative risks (RRs) for multiple infections and respiratory complications between cohorts during the observation period.¹⁵ All analyses were performed using STATA, version 14 (StataCorp, College Station, TX, <http://www.stata.com/>).

RESULTS

The sex and age distribution among all three groups was similar by design (Table 1). The median age at HCT was 47 years (interquartile range, 31 to 57), similar to the median ages of the non-HCT group at cancer diagnosis (49 years; interquartile range, 34 to 58 years) and the DOL group (48 years; interquartile range, 37 to 57 years). Among individuals not known to be deceased, the three groups had similar median follow-up duration (HCT: 7.1 years; non-HCT: 7.2 years; and DOL: 7.7 years; range, 2 to 20 years for all three groups). Within the HCT group, the median time from original disease diagnosis to transplantation was 9.3 months (interquartile range, 5.7 to 19.7 months). A total of 143 HCT survivors (8.0%) also received a subsequent transplant before reaching the 2-year survival landmark.

Table 1. Demographic and Treatment Characteristics of ≥ 2 -Year HCT Survivors and Comparison Cohorts (non-HCT cancer survivors; general population, DOL)

Characteristic	HCT (N = 1,792)		Non-HCT (N = 5,455)*		DOL (N = 16,340)†	
	No.	%	No.	%	No.	%
Female sex	819	45.7	2,381	43.6	7,500	45.9
Race/ethnicity						
White non-Hispanic	1,504	83.9	4,543	83.3	—	—
Black	40	2.2	202	3.7	—	—
Hispanic	81	4.5	270	4.9	—	—
Asian	75	4.2	241	4.4	—	—
Other/unknown	92	5.1	199	3.6	—	—
Age at index date, years‡						
< 20	277	15.5	767	14.1	570	3.5
20-39	376	21.0	934	17.1	4,100	25.1
40-59	843	47.0	2,590	47.5	8,660	53.0
≥ 60	296	16.5	1,164	21.3	3,010	18.4
Year of index event						
1992-1999	520	29.0	1,417	26.0	4,480	27.4
2000-2009	1,272	71.0	4,038	74.0	11,860	72.6
Diagnosis category§						
Hematologic malignancy	1,617	90.2	4,808	88.1	—	—
Nonhematologic solid tumor	175	9.8	647	11.9	—	—
Donor type						
Autologous/isogeneic	867	48.4	—	—	—	—
Related allogeneic	503	28.1	—	—	—	—
Unrelated allogeneic	422	23.5	—	—	—	—
History of total body irradiation						
None	969	54.1	—	—	—	—
< 10 Gy	221	12.3	—	—	—	—
≥ 10 Gy	602	33.6	—	—	—	—
History of chronic GVHD	642	36.1	—	—	—	—
History of cancer relapse after index date	434	24.2	—	—	—	—
Died during the follow-up period	388	21.7	997	18.3	581	3.6

Abbreviations: —, no data; DOL, Department of Licensing; GVHD, graft versus host disease; HCT, hematopoietic cell transplantation.

*Matched on 3:1 basis by sex, and age at and year of HCT or cancer diagnosis to HCT survivors. Data on relapse status are not collected by the state cancer registry.

†Matched on 10:1 basis by sex, and age at and year of HCT or driver licensing to HCT survivors age ≥ 16 years at time of transplantation. Race and ethnicity data not available.

‡Age at transplant (HCT survivors), initial cancer diagnosis (non-HCT cancer survivors), or driver licensing (general population).

§A more detailed breakdown of diagnoses is given in the Data Supplement.

|| Limited to those who required systemic immunosuppressive therapy (n = 14 with unknown status).

The 10-year cumulative incidence of any hospitalization or death related to all major organ-system outcomes was significantly different ($P < .05$) between the HCT and DOL groups (Fig 1; Data Supplement). Differences in cumulative incidences between the HCT and non-HCT groups were less pronounced. The HCT group

notably had a 30.6% cumulative incidence of infectious complications (difference ν non-HCT: 8.7%, 95% CI 5.9% to 11.6%) and a 26.8% incidence of any respiratory complications (difference ν non-HCT: 6.9%, 95% CI 4.2% to 9.6%). The 10-year cumulative incidences of nervous system, circulatory, and genitourinary

Fig 1. Ten-year cumulative incidence with 95% CIs (spikes) of major outcomes among ≥ 2 -year HCT survivors and comparison cohorts (non-HCT cancer survivors; general population, DOL). Incidence of pregnancy was limited to women ages 15 to 44 years during the observation period. Subsequent new cancers were only ascertained among HCT and non-HCT cancer survivors. * $P < .05$ for differences between HCT ν non-HCT. † $P < .05$ for differences between HCT ν DOL and non-HCT ν DOL, limited to individuals age ≥ 16 years. ‡ $P < .05$ for difference between HCT ν DOL only. DOL, Department of Licensing; HCT, hematopoietic cell transplantation.

complications, mental health outcomes, and subsequent new cancers were similar between the HCT and non-HCT groups. Among women ages 15 to 44 years, the incidence of pregnancy-related hospitalization was lower in the HCT group versus the non-HCT group (difference, -4.4%, 95% CI, -8.4 to -0.4%).

Adjusted analyses starting at the 2-year landmark showed that certain risks were notably higher in the HCT group versus the non-HCT group (Table 2). These included primary infections (HR, 1.4; 95% CI, 1.2 to 1.6), respiratory complications (HR, 1.3; 95% CI, 1.2 to 1.5), and death from any cause (HR, 1.1; 95% CI, 1.01 to 1.3). Risks of hospitalization for nervous system, circulatory, digestive, and genitourinary complications, and mental health conditions were similar (HR range, 0.9 to 1.1; $P > .05$). The risk of subsequent cancers, based on state cancer registry data, also was similar in the two groups. For most outcomes, the relative hazards associated with HCT tended to increase for most outcomes beyond 5 years of follow-up (Table 2). Among ≥ 2 -year female survivors, the likelihood of pregnancy-associated hospitalizations was lower in the HCT group ($n = 5$) versus the non-HCT group ($n = 46$; HR, 0.1, 95% CI, 0.01 to 0.6 for ages 15 to 29 years; HR, 0.5, 95% CI, 0.1 to 1.5 for ages 30 to 44 years). Finally, comparisons of HCT with non-HCT survivors adjusted for donor type (ie, autologous, allogeneic) generally showed similar results (Data Supplement). Results restricted to hematologic malignancies also generally showed similar results (data not shown), although risks of specific outcomes did appear to vary somewhat when cancer diagnostic groups were examined individually (Data Supplement).

Among organ system-specific infection categories, the HCT group was more likely to experience infections of the nervous system (HR, 2.5; 95% CI, 1.4 to 4.6; most commonly meningitis), respiratory system (HR, 1.6; 95% CI, 1.4 to 1.9; most commonly pneumonia), and the digestive tract (HR, 1.7; 95% CI, 1.2 to 2.5; most commonly oral, gastrointestinal, and biliary infections) compared with the non-HCT group. The risk of noninfectious respiratory complications (ie, chronic obstructive pulmonary

disease, asthma, pulmonary fibrosis, and pneumonopathy) also was greater in the HCT group versus the non-HCT group (HR, 1.3; 95% CI, 1.1 to 1.5). Poisson models that allowed for multiple events confirmed greater risks of primary infections (RR, 1.6; 95% CI, 1.3 to 1.9) and respiratory complications (RR, 1.7; 95% CI, 1.4 to 2.0) in the HCT group compared with the non-HCT group.

The HCT group overall had a significantly greater hospitalization rate compared with the non-HCT group (280 episodes per 1,000 person-years v 173 episodes per 1,000 person-years; $P < .001$). When selected hospitalization discharge diagnoses were examined, the proportions of patients with a primary infectious, respiratory, or musculoskeletal condition diagnosis appeared similar for the HCT and non-HCT groups (Table 3; Data Supplement).

Among subsequent cancers reported within the HCT group ($n = 128$ cancers) and non-HCT group ($n = 438$ cancers), 107 (83.6%) and 304 (69.4%) cancers occurred after 1 year, respectively, with $> 85\%$ in both groups being malignant versus benign or in situ tumors (Data Supplement). Among cancers diagnosed in at least four individuals after the 2-year landmark, the HCT group had greater risks of oral cancers (HR, 5.4; 95% CI, 1.6 to 18.4) and skin cancers compared with the non-HCT group (HR, 4.9; 95% CI, 1.9 to 12.7; primarily melanoma, because squamous and basal cell carcinomas were not ascertained).

Within the HCT group, the risks of morbidity and mortality outcomes for most outcome categories were significantly and independently associated with chronic GVHD and relapse of the original disease, but not with donor type (Table 4). In analyses restricted to events occurring ≥ 5 years after the index transplantation, a history of chronic GVHD remained significantly associated with greater risks of primary infections and respiratory and genitourinary conditions. Chronic GVHD also appeared to be associated with greater risks of new cancers, but HR estimates were imprecise and were not statistically significant. When history of TBI was added to the analyses (data not shown), those who had received TBI < 10 Gy experienced a greater burden of infectious

Table 2. Relative HRs of Major Outcomes Among HCT Survivors Versus Non-HCT Cancer Survivors

Outcome	Events ≥ 2 years*			Events ≥ 5 years*		
	No. Affected: HCT ($n = 1,792$)/ non-HCT ($n = 5,455$)	HR†	95% CI	No. Affected: HCT ($n = 1,102$)/ non-HCT ($n = 3,386$)	HR†	95% CI
Infections, all	471/1,017	1.4	1.3 to 1.6	174/344	1.6	1.3 to 1.9
Infections, primary	333/694	1.4	1.2 to 1.6	123/220	1.8	1.4 to 2.2
Nervous system	206/567	1.1	0.9 to 1.3	88/228	1.2	0.96 to 1.6
Circulatory	401/1,122	1.0	0.9 to 1.2	178/477	1.1	0.9 to 1.3
Respiratory	407/912	1.4	1.2 to 1.5	160/334	1.5	1.2 to 1.8
Digestive	302/792	1.1	0.99 to 1.3	119/309	1.2	0.98 to 1.5
Genitourinary	288/764	1.1	0.96 to 1.3	120/290	1.2	0.98 to 1.5
Skin	118/276	1.3	1.0 to 1.6	43/103	1.3	0.9 to 1.8
Musculoskeletal	272/641	1.3	1.1 to 1.5	117/264	1.4	1.2 to 1.8
Mental health‡	105/357	0.9	0.7 to 1.1	52/183	0.9	0.6 to 1.2
New cancers, all	99/287	1.1	0.9 to 1.4	62/163	1.2	0.9 to 1.7
New cancers, malignant	89/260	1.1	0.9 to 1.4	52/148	1.1	0.8 to 1.6
Death, all causes	388/997	1.1	1.0 to 1.3	140/342	1.2	1.0 to 1.5

Abbreviations: HCT, hematopoietic cell transplantation; HR, hazard ratio.

*From index event onward.

†All models adjusted for sex, year of index event (HCT or cancer diagnosis), and underlying diagnosis group on an age timescale.

‡Limited to events occurring at age ≥ 18 years; to satisfy proportional hazard assumptions, values shown are for 2-4.9 years and 5-9.9 years from index event, respectively; 30 HCT and 64 non-HCT subjects had mental health outcomes recorded beyond 10 years (HR, 1.6; 95% CI, 0.98 to 2.5).

Table 3. Distribution of the Selected Hospitalization Discharge Diagnoses Within Selected Organ-System Categories Among HCT and Non-HCT Cancer Survivors

Diagnosis Category	HCT, Hospitalizations*			Non-HCT, Hospitalizations*		
	No. (N = 2,858)	Organ-System Hospitalizations (%)	Total Hospitalizations (%)	No. (N = 5,473)	Organ-System Hospitalizations (%)	Total Hospitalizations (%)
Infections, primary	639	—	22.4	1,169	—	21.4
Bacteria	310	48.5	10.8	572	48.9	10.5
Viral	187	29.3	6.5	329	28.1	6.0
Fungal	139	21.8	4.9	238	20.4	4.3
Any sepsis	189	29.6	6.6	381	32.6	7.0
Respiratory	843	—	29.5	1,637	—	29.9
Pneumonia	389	46.1	13.6	612	37.4	11.2
Chronic obstructive disease	99	11.7	3.5	414	25.3	7.6
Fibrosis	47	5.6	1.6	61	3.7	1.1
Any respiratory failure	174	20.6	6.1	354	21.6	6.5
Circulatory	857	—	30.0	2,441	—	44.6
Ischemia/atherosclerosis	85	9.9	3.0	533	21.8	9.7
Cardiomyopathy/heart failure	146	17.0	5.1	580	23.8	10.6
Cerebrovascular accident/stroke	43	5.0	1.5	135	5.5	2.5
Other thrombosis	81	9.5	2.8	130	5.3	2.4
Arrhythmia	171	20.0	6.0	653	26.8	11.9
Hypertension	407	47.5	14.2	1,276	52.3	23.3
Musculoskeletal	494	—	17.3	1,031	—	18.8
Fracture	81	16.4	2.8	231	22.4	4.2
Pathologic	42	8.5	1.5	106	10.3	1.9
Other	40	8.1	1.4	129	12.5	2.4
Avascular necrosis	81	16.4	2.8	61	5.9	1.1

Abbreviations: —, not applicable; HCT, hematopoietic cell transplantation.

*Limited to hospitalizations occurring ≥ 2 years after index date. Each hospitalization may contain multiple codes, and some participants had multiple hospitalizations. Specific codes corresponding to each category are listed in the Data Supplement.

and respiratory complications 2 years after transplant versus survivors without TBI (HR range, 1.6 to 1.7; $P < .01$). In contrast, survivors treated with TBI ≥ 10 Gy did not experience more infectious or respiratory complications than those without TBI, but had a greater risk of new cancers after 2 years (HR range, 2.3 to 2.5; $P < .01$). Receipt of more than one HCT before 2-year survival was not associated with an increased hazard of any subsequent outcome (data not shown).

DISCUSSION

We found that HCT survivors experienced a significantly greater burden of hospitalizations and mortality compared with matched non-HCT cancer survivors. Disparities in infectious and respiratory complications were marked, whereas the burden of circulatory disease, mental health diagnoses, and second cancers appeared similar between

Table 4. Demographic and Treatment-Related Risk Factors for Major Outcomes After 2 Years (n = 1,792) and After 5 Years (n = 1,102) Among HCT Survivors*

Outcome	Events ≥ 2 Years						Events ≥ 5 Years					
	Allogeneic v Autologous		Chronic GVHD v None†		Original Disease Relapse v None		Allogeneic v Autologous		Chronic GVHD v None†		Original Disease Relapse v None	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Infection, all	0.9	0.7 to 1.3	1.5	1.1 to 2.0	2.4	1.9 to 3.0	0.8	0.5 to 1.3	1.2	0.8 to 2.0	2.3	1.6 to 3.2
Infection, primary	0.8	0.5 to 1.2	1.7	1.2 to 2.4	2.8	2.1 to 3.6	0.5	0.3 to 0.96	2.0	1.04 to 3.9	2.6	1.8 to 3.8
Nervous system	0.5	0.3 to 0.8	2.5	1.4 to 4.3	2.6	1.8 to 3.6	0.4	0.2 to 0.9	2.0	0.8 to 4.7	2.4	1.5 to 3.8
Circulatory	0.7	0.5 to 1.0	1.6	1.1 to 2.2	2.0	1.5 to 2.5	0.9	0.6 to 1.5	1.3	0.8 to 2.1	2.1	1.5 to 3.0
Respiratory	0.8	0.6 to 1.1	1.7	1.2 to 2.4	2.0	1.6 to 2.6	0.6	0.3 to 1.1	2.0	1.1 to 3.5	2.2	1.5 to 3.1
Digestive	0.7	0.5 to 1.1	1.6	1.1 to 2.4	2.3	1.7 to 3.0	0.7	0.4 to 1.3	1.6	0.9 to 3.0	2.1	1.4 to 3.2
Genitourinary	0.8	0.5 to 1.2	1.7	1.2 to 2.6	2.2	1.7 to 3.0	0.6	0.3 to 1.3	2.2	1.1 to 4.2	2.3	1.5 to 3.5
Skin	1.1	0.6 to 1.9	1.5	0.9 to 2.7	2.3	1.4 to 3.6	1.3	0.5 to 3.0	0.9	0.4 to 2.1	2.3	1.2 to 4.5
Musculoskeletal	0.8	0.5 to 1.3	1.9	1.2 to 2.9	1.4	0.99 to 2.0	0.7	0.4 to 1.3	1.4	0.8 to 2.5	2.1	1.4 to 3.2
Mental health‡	1.0	0.6 to 1.5	0.9	0.9 to 1.0§	2.4	1.6 to 3.4	1.3	0.7 to 2.4	0.6	0.3 to 1.2	1.6	0.9 to 2.7
New cancers, all	0.7	0.4 to 1.5	1.7	0.8 to 3.5	1.1	0.6 to 2.1	0.6	0.2 to 1.6	2.5	0.9 to 6.4	0.9	0.4 to 1.8
New cancers, malignant	0.8	0.4 to 1.7	1.4	0.6 to 2.8	1.3	0.7 to 2.4	0.6	0.2 to 1.7	2.3	0.8 to 6.7	1.1	0.5 to 2.3

Abbreviations: GVHD, graft versus host disease; HR, hazard ratio.

*Models all adjusted for sex, race and ethnicity, and age at and year of transplantation, donor type, history of chronic GVHD, and history of original disease relapse.

†Limited to those who required systemic immunosuppressive therapy.

‡Limited to those age ≥ 18 years.

§Chronic GVHD modeled as time-varying to meet proportional hazard assumptions.

these two groups. In general, differences were magnified when the analysis was limited to adverse events occurring ≥ 5 years after the index date, thereby reducing the contribution related to the acute toxicities of treatment, original disease relapse, and active chronic GVHD. A major strength of this study is its reliance on prospectively coded and population-based data sources free of response biases.

We previously used statewide registry data to examine cardiovascular hospitalizations and mortality and found greater absolute and relative risks when HCT survivors were compared with the general population.¹¹ The current analysis is more nuanced and showed that the risks for cardiovascular disease, at least overall, may not differ between HCT survivors and matched non-HCT cancer survivors. Similarly, we did not find a significantly different overall risk of second cancers, although specific cancers affecting the skin (primarily melanoma) and the oral cavity were more common among HCT survivors than non-HCT cancer survivors. Exposures unique to HCT survivors, such as chronic GVHD, may be responsible for the greater risks of these specific tumor types.¹⁶ Such distinctions are important because clinicians have hypothesized that HCT survivors may be at greater risk for long-term health complications compared with other cancer survivors, and may require additional surveillance or health counseling beyond those recommended for other cancer survivors. Our analysis provided additional context regarding those organ systems and outcome categories where this hypothesis may be correct and others where this hypothesis may be less compelling.

Few comprehensive analyses have compared HCT with non-HCT cancer survivors. A report examining survivors of childhood HCT compared with non-HCT survivors of childhood hematologic malignancies showed that HCT survivors had a nearly four-times greater risk of self-reported severe or life-threatening chronic conditions, including second cancers, endocrine conditions, and musculoskeletal conditions.¹⁷ TBI and any history of chronic GVHD (active or resolved) were associated with the development of more severe chronic conditions. Relative differences in second-cancer risk between our studies could be related, in part, to the composition of study participants (ie, childhood v mostly adult-onset cancer survivors). It also is possible that the experiences of survivors treated at other institutions and other geographic regions may differ from our findings.

Studies also have shown that HCT survivors often have pulmonary dysfunction, including both restrictive and obstructive disease.^{18,19} A subset of allogeneic survivors develop bronchiolitis obliterans syndrome, which is characterized by chronic irreversible airflow obstruction and is associated with chronic GVHD.²⁰ Other risk factors for pulmonary dysfunction after HCT include a history of TBI and respiratory viral infections.^{18,19} Although most studies suggest that pulmonary function abnormalities increase over time,^{19,21} some degree of recovery may be possible.²² Current guidelines recommend that survivors of autologous HCT and allogeneic HCT be screened annually with a history and physical examination for pulmonary dysfunction,³ with consideration of more frequent pulmonary function testing among survivors with chronic GVHD.²³ Our results would support this recommendation.

Immunity is altered as a direct consequence of HCT, and immune reconstitution may be further disrupted by GVHD and long-term immunosuppression.²⁴⁻²⁶ Although current guidelines on antimicrobial prophylaxis and reimmunization primarily focus on patients with chronic GVHD,³ our results suggest that even those without chronic GVHD, including autologous HCT survivors, remain at

increased risk long term. This finding corroborates prior studies showing that infection remains a leading cause of death, even in the absence of GVHD, among ≥ 2 -year allogeneic HCT survivors, including ≥ 5 or ≥ 10 -year survivors.^{8,10} Studies of pediatric autologous HCT recipients have shown that immune reconstitution, in particular T-cell recovery, may be abnormal even 2 or more years after HCT.²⁷

Other findings in our study include a reduced likelihood of pregnancy-related hospitalizations compared with non-HCT female cancer survivors, but an overall similar risk of mental health conditions between the two groups. Both TBI and high-dose alkylating agents (eg, cyclophosphamide, busulfan) used as part of the conditioning regimen are associated with adverse effects on fertility.²⁸⁻³⁰ Whereas HCT survivors had similar rates of mental health conditions compared with non-HCT survivors, the burden of these conditions was greater compared with the general population. A similar increased burden among HCT survivors versus siblings has been reported.³¹ However, psychological health may improve over time for many HCT survivors.³²

Our results should be interpreted with some considerations. Although we specifically matched HCT with non-HCT cancer survivors by original diagnosis, sex, and age at and year of HCT or cancer diagnosis, we could not account for pre-existing comorbidities or cancer treatment exposures that occurred before HCT and those received by the non-HCT group. Some of the differences between groups may be due to more advanced disease and more pre-HCT cancer treatment exposures in HCT recipients. At the same time, prerequisites for adequate organ function may be more stringent for HCT candidates,³³ which may minimize differences between HCT and non-HCT survivors. Future analyses that focus on specific outcome categories could attempt to reconstruct exposures such as radiation and chemotherapy received before HCT, as well as pre-existing comorbidities.

Although a strength of our analysis is the lack of response bias, misclassification of outcomes can still occur when using registry and administrative databases. However, any misclassification should apply similarly across groups and would be expected to bias results toward the null. In general-population studies, the specificity of hospital discharge and other administrative datasets is typically more than 90%, but sensitivity can be more variable compared with chart review.³⁴⁻³⁸ However, longitudinal hospitalization data of the type we used can improve sensitivity without reducing specificity.³⁵ Finally, because HCT survivors were hospitalized more frequently than non-HCT cancer survivors, they would have had more opportunities to have diagnoses recorded. We did not find that HCT survivors had a consistently greater burden of all late outcomes compared with non-HCT survivors, arguing against systematic measurement bias. Even so, less severe conditions that did not result in hospitalizations would not have been ascertained in this analysis, but may still affect quality of life.

In summary, we found that HCT survivors were generally at greater risk for all categories of late outcomes compared with the general population. Differences between HCT survivors and matched non-HCT cancer survivors were less pronounced, with the exception of late infections and respiratory (both infectious and noninfectious) complications. Clinicians who care for long-term survivors of HCT should be aware of comprehensive surveillance guidelines available for this high-risk population.^{3,4,16} Future work to identify more specific risk factors associated with late infections and respiratory complications may help to further refine these guidelines and identify new prevention strategies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Morbidity and Mortality Differences Between Hematopoietic Cell Transplantation Survivors and Other Cancer Survivors**

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