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Risk of Secondary Malignancies in Hematopoietic Stem Cell Transplantation Recipients: A Nationwide Population-Based Study in Taiwan

Hsi-Ling Liu[1], Yi-Hsien Chen[1], Chi-Hsiang Chung[2,3,4], Gwo-Jang Wu[3,5,6], Chang-Huei Tsao[3,7], Chien-An Sun[8,9], Wu-Chien Chien[2,3,4,10]*, Chih-Tsung Hung[1,5]*

[1]Department of Dermatology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
[2]School of Public Health, National Defense Medical Center, Taipei, Taiwan
[3]Department of Medical Research, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
[4]Taiwanese Injury Prevention and Safety Promotion Association, Taipei, Taiwan
[5]Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan
[6]Department of Obstetrics and Gynecology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
[7]Department of Microbiology and Immunology, National Defense Medical Center, Taipei, Taiwan
[8]Department of Public Health, College of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan
[9]Big Data Research Center, College of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan
[10]Graduate Institute of Life Sciences, National Defense Medical Center, Taipei, Taiwan

**These authors contributed equally to this work.*

Background: The improvement of survival after hematopoietic stem cell transplantation has brought about a need to evaluate long-term complications, for instance, secondary malignancies. The risk of subsequent malignancies after hematopoietic stem cell transplantation must be clarified in a large population.

Aims: To estimate the risk of secondary malignancies in hematopoietic stem cell transplantation survivors and compare it with the risk in patients without hematopoietic stem cell transplantation history.

Study Design: We conducted a population-based retrospective cohort study of 3,059 hematopoietic stem cell transplantation recipients from the National Health Insurance Research Database of Taiwan, containing 1,378 autologous, 1,641 allogeneic, and 40 cord blood stem cell transplantation recipients between 2000 and 2013. A control group of 12,236 patients without an hematopoietic stem cell transplantation history was identified.

Methods: The covariates included age, sex, comorbidities, stem cell source, facility level of care, and history of total body irradiation. Comorbidities were estimated by the revised Charlson comorbidity index, and a higher score suggested more severe comorbidity. Adjusted hazard ratios were determined by adjusting for age, sex, comorbidity, and facility level of care.

Results: Overall, hematopoietic stem cell transplantation recipients had a higher risk of secondary malignancies with an adjusted hazard ratios of 1.348 ($p = 0.017$). Being male and female (adjusted hazard ratios 1.395, $p = 0.009$ and adjusted hazard ratios 1.291, $p = 0.042$, respectively) and pre-hematopoietic stem cell transplantation total body irradiation (adjusted hazard ratios 1.591, $p < 0.001$) were correlated with a high risk of secondary malignancies. Among the subsequent neoplasms, bone cancer showed the highest risk (adjusted hazard ratios 27.899, $p < 0.001$), followed by laryngeal (adjusted hazard ratios 6.643, $p < 0.001$), kidney (adjusted hazard ratios 5.580, $p < 0.001$), esophageal, pancreatic, thyroid (adjusted hazard ratios 1.993,

Corresponding author: Wu-Chien Chien, School of Public Health, National Defense Medical Center, Taipei, Taiwan; Chih-Tsung Hung, Department of Dermatology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
e-mail: chienwu@ndmctsgh.edu.tw; barrypig72@hotmail.com

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ORCID iDs of the authors: H-L.L. 0000-0002-2961-5071; Y-H.C. 0000-0002-7019-2357; C-H.C. 0000-0002-4576-9900; G-J.W. 0000-0001-5360-8018; C-H.T. 0000-0003-2982-3732; C-A.S. 0000-0001-9041-0537; W-C.C. 0000-0002-3286-0780; C-T.H. 0000-0001-7138-7757.

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$p < 0.001$), and skin (adjusted hazard ratios 1.992, $p < 0.001$) cancers. The median follow-up duration was 2.16 years in the hematopoietic stem cell transplantation group and 2.57 years in the control group, and the overall median follow-up duration was 2.21 years.

Conclusion: Medical practitioners should be aware of the high risk of secondary malignancies in hematopoietic stem cell transplantation recipients later in life. These recipients should be informed about the importance of regular follow-up and photoprotective measures. Lifelong surveillance is recommended.

INTRODUCTION

The number of survivors after successful hematopoietic stem cell transplantation (HSCT) has increased ever since the wide use of HSCT in treating malignant and nonmalignant diseases. Awareness of long-term complications is increasing among researchers and health professionals.[1] With an incidence being eightfold above the general population, secondary malignancies have been perceived as one of the most severe sequelae.[2] Several risk factors have been proposed, such as radiotherapy and chemotherapy as a part of pre-transplantation conditioning and treatment of the primary malignancy, slowed convalescence of immune system-related immunodeficiency, immune system alterations owing to graft versus host disease (GVHD), and immunosuppressants prescribed for GVHD.[2] Patients who underwent HSCT endure a high risk of secondary solid malignancies throughout life.[3] Overall, these individuals developed secondary solid malignancies with a twofold risk higher than the general population and a threefold risk over 15 years after transplantation.[4] In the past few years, several studies have suggested that HSCT survivors were associated with high risks of developing subsequent secondary malignancies. However, large population-based studies in Asia are insufficient. Thus, we attempted to investigate the association between HSCT recipients and the subsequent secondary malignancies in a nationwide cohort study of a Taiwanese population, examine the risk of each cancer type in HSCT survivors, and evaluate the cancer risk among different HSCT sources.

MATERIALS AND METHODS

Data Acquisition

This retrospective cohort study utilized comprehensive healthcare data accessed from the National Health Insurance Research Database (NHIRD) of Taiwan. Moreover, 99% of the Taiwanese population were enrolled in the Taiwanese National Health Insurance (NHI), which was a compulsory-enrollment and single-payer social insurance. Researchers were allowed access to each enrollee's anonymized registration records, including ambulatory care, inpatient data, emergency data, and diagnostic codes for academic purposes using an undisclosed identification code. The diagnostic codes of HSCT and malignancies designated by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) were identified between 2000 and 2013.

Study Participants

A total of 15,295 patients from the NHIRD between 2000 and 2013 in Taiwan were identified for this retrospective study. HSCT recipient data between 2000 and 2013 were obtained, consisting of autologous (OP41.04, OP41.07, and OP41.09), allogeneic (OP41.05 and OP41.08), and cord blood stem cell transplantation (CBSCT) (OP41.06) recipients. Patients with previous malignancies, unknown age, or sex and those who were lost to follow-up were excluded in both the study cohort and control groups. The sex, age, and index date of the control group were matched with those of the study group. Finally, 3,059 patients in the study group and 12,236 individuals in the control group were enrolled in this study (Figure 1).

Outcome Measures

This study traced all the patients from the index date, date of transplantation for the HSCT group, and beginning of follow-up for controls until the commencement of secondary malignancies, dropout from the NHI program, or end of 2013. Secondary malignancies were identified by adopting the ICD-9-CM code of 135-154 for colorectal cancer, 155-157 for liver, gall bladder, and pancreatic cancer, 161-162 for laryngeal and lung cancer, 170 for bone cancer, 172 for skin melanoma, 173 for malignant neoplasm of the skin, 174-175 for female and male breast cancer, 176 for cutaneous Kaposi sarcoma, 179-180 for uterus and cervical uterine cancer, 182 for corpus uterine cancer, 185 for prostate cancer, 188-189 for bladder and kidney cancer, and 193 for thyroid cancer.

Covariates

The covariates included stem cell source, age, sex, comorbidities, level of care (hospital center, regional hospital, and local hospital), and history of total body irradiation (TBI). The revised Charlson Comorbidity Index (CCI-R) was applied to weigh the comorbidities. The CCI is a sum up of the score estimated by categorizing a list of comorbidities into several groups and the score of each group.[5] A higher score suggests more complex comorbidity, whereas a score of zero is regarded as no comorbidities. CCI-R was defined as CCI excluding malignancies because this study aimed to evaluate malignancies post-HSCT.

Statistical Analysis

IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA) was used to analyze data. The chi-squared and Fisher's exact tests were used to compare baseline categorical covariates between the HSCT group and the control group, whereas Student's t-test was used to appraise continuous variables. The incidence (per 10^5 person-years) was determined using the number of patients with incident secondary malignancies divided by the total person-years in each cohort. The hazard ratios (HRs) and 95%

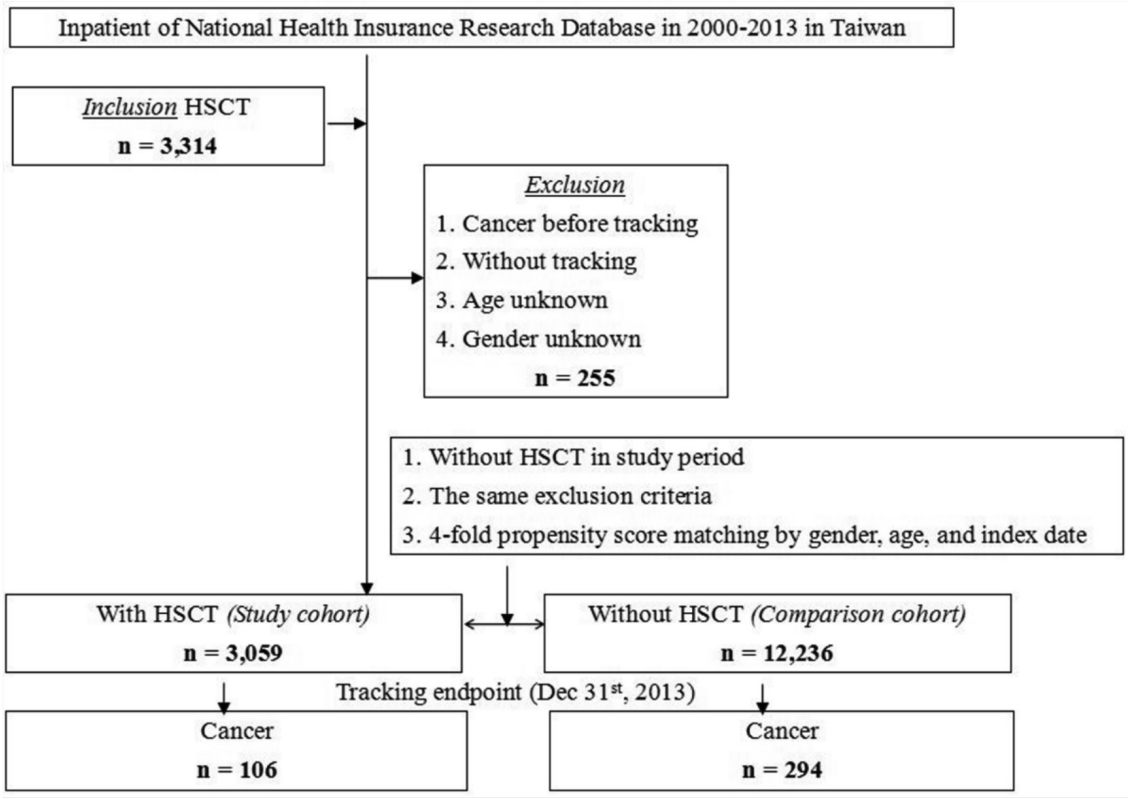

FIG. 1. The flowchart of study population selection. Our study included 3,059 patents with hematopoietic stem cell transplantation (HSCT) and 12,236 matched patients without HSCT. HSCT, hematopoietic stem cell transplantation.

confidence intervals (CIs) were obtained through a multivariable Cox regression model. The cumulative incidence of secondary malignancies in HSCT recipients was estimated by Kaplan-Meier analysis and log-rank test.

RESULTS

A total of 3,059 HSCT recipients and 12,236 patients without HSCT history from 2000 to 2013 were enrolled in this study. The median follow-up duration was 2.16 years in the HSCT group, 2.57 years in the control group, and the overall median follow-up duration was 2.21 years (Table S1). The sex and age were comparable between the HSCT group and the control group, whereas the CCI demonstrated a significant difference ($p < 0.001$) between the two groups (Table 1). At the study endpoint, 106 patients developed malignant neoplasms in the HSCT group and 294 patients developed malignancies in the non-HSCT group (Figure 1). The HSCT group was inclined to have a greater risk of secondary cancers than those who did not receive HSCT (Table 2; $p = 0.001$).

Cumulative Risk of Cancer Incidence with Kaplan-Meier Model

In the 7th year, the incidence of cancer had been higher in the HSCT group ($p = 0.026$; Table S2), and this condition persisted until the end of the follow-up (Figure 2; Table S2). Of the three

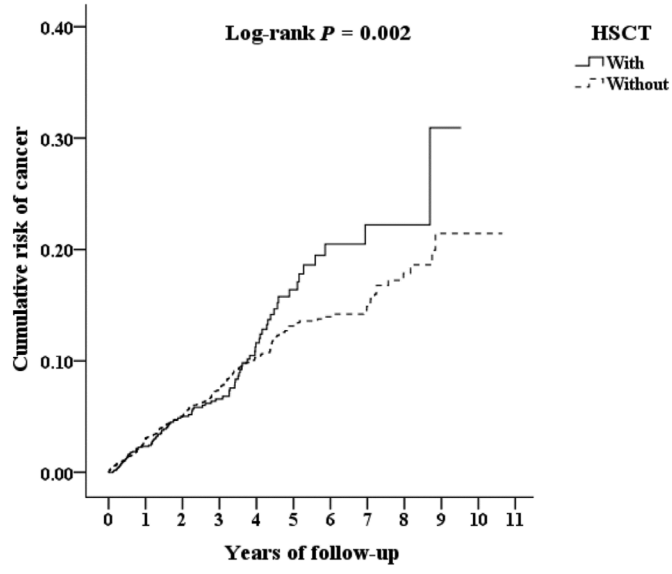

FIG. 2. Kaplan-Meier for cumulative risk of cancer stratified by HSCT with log-rank test. The cumulative risks of secondary cancer were higher in the HSCT cohort than in the control cohort; this pattern continued until the end of the follow-up period (log-rank; $p = 0.002$). HSCT, hematopoietic stem cell transplantation.

HSCT subtypes, the autologous group had the highest incidence of secondary malignancies (Figure S1). The mean duration from the beginning of follow-up to the incidence of secondary malignancies was 2.05 ± 1.79 years for the HSCT group and 2.08 ± 1.82 years for the control group (Table S3).

HR of Cancer Occurrence in the HSCT Group

Covariates including age, sex, level of care, and comorbidity were adjusted. The HSCT group had a significantly high risk of malignancies (adjusted HR 1.348; 95% CI, 1.055-1.721; p = 0.017; Table 3). Factors that affect general malignant neoplasm, including sex and level of care, were further stratified. The male and female groups of the HSCT group showed a significant risk of secondary malignancies (adjusted HR 1.395; 95% CI, 1.092-1.781; p = 0.009 and adjusted HR 1.291; 95% CI, 1.010-1.648; p = 0.042, respectively; Table 3). Among the three hospital facility levels, those having treatment at hospital centers had the highest adjusted HR of subsequent malignancies (adjusted HR 1.475; 95% CI, 1.160-1.876; p < 0.001; Table 3).

HR Analysis of Cancer Rates Among HSCT Subgroups

Among HSCT sources, the autologous type was identified to have a significantly higher incidence of secondary malignancies (adjusted HR 1.533; 95% CI, 1.148-2.046; p = 0.004, Table 4).

TABLE 1. Characteristics at Baseline.

	Total		With HSCT		Without HSCT		
Variables	n	%	n	%	n	%	*p*
Total	15,295		3,059	20.00	12,236	80.00	
Sex							0.999
Male	8,635	56.46	1,727	56.46	6,908	56.46	
Female	6,660	43.54	1,332	43.54	5,328	43.54	
Age (years)	38.53 ± 18.11		38.11 ± 17.00		38.64 ± 18.37		0.148
CCI	0.21 ± 0.63		0.12 ± 0.41		0.23 ± 0.67		<0.001
Level of care							<0.001
Hospital center	6,879	44.98	2,821	92.22	4,058	33.16	
Regional hospital	5,855	38.28	238	7.78	5,617	45.91	
Local hospital	2,561	16.74	0	0.00	2,561	20.93	

HSCT, hematopoietic stem cell transplantation. p: χ2-test/Fisher's exact test for category variables, whereas Student's t-test for continuous variables. CCI-R, revised edition of the Charlson comorbidity index

TABLE 2. Characteristics at Endpoint.

	Total		With HSCT		Without HSCT		
Variables	n	%	n	%	n	%	p
Total	15,295		3,059	20.00	12,236	80.00	
Cancer							0.001
Without	14,895	97.38	2,953	96.53	11,942	97.60	
With	400	2.62	106	3.47	294	2.40	
Sex							0.999
Male	8,635	56.46	1,727	56.46	6,908	56.46	
Female	6,660	43.54	1,332	43.54	5,328	43.54	
Age (years)	43.88 ± 20.31		43.22 ± 17.89		44.04 ± 20.87		0.046
CCI_R	0.27 ± 0.71		0.23 ± 0.62		0.28 ± 0.73		<0.001
Level of care							<0.001
Hospital center	6,750	44.13	2,494	81.53	4,256	34.78	
Regional hospital	6,038	39.48	472	15.43	5,566	45.49	
Local hospital	2,507	16.39	93	3.04	2,414	19.73	
All-cause mortality							<0.001
Without	14,258	93.22	2,305	75.35	11,953	97.69	
With	1,037	6.78	754	24.65	283	2.31	

HSCT, hematopoietic stem cell transplantation; p: χ2-test/Fisher's exact test for category variables, whereas Student's t-test for continuous variables. CCI-R, revised edition of the Charlson comorbidity index

Allogeneic HSCT and CBSCT were not risk factors for secondary malignancies (adjusted HR 1.286; 95% CI, 0.920-1.797; $p = 0.141$ and 2/40, $p = 0.081$, respectively; Table 4). HSCT with TBI was also significantly related to secondary malignancies (adjusted HR 1.419; 95% CI, 1.104-1.823; $p = 0.006$; Table 4), whereas HSCT without TBI did not reach statistical significance (adjusted HR 1.577; 95% CI, 0.924-2.693; $p = 0.095$; Table 4).

HR of HSCT and Subsequent Malignant Neoplasms

Overall, a high risk of cancer occurrence after HSCT was found. Further stratified risk analyses of different malignant neoplasms revealed bone cancer as having the most significant risk in the HSCT group (adjusted HR 27.899; 95% CI, 21.939-35.471; $p < 0.001$), followed by laryngeal (adjusted HR 6.643; 95% CI, 5.224-8.446; $p < 0.001$), kidney (adjusted HR 5.580; 95% CI, 4.388-7.094; $p < 0.001$), corpus uteri (adjusted HR 3.986; 95% CI, 3.134-5.067; $p < 0.001$), esophageal, pancreatic, thyroid (adjusted HR 1.993; 95% CI, 1.567-2.534; $p < 0.001$), skin (adjusted HR 1.992; 95% CI, 1.565-2.531; $p < 0.001$), colorectal (adjusted HR 1.724; 95% CI, 1.355-2.191; $p < 0.001$), female breast (adjusted HR 1.55; 95% CI, 1.219-1.971; $p < 0.001$), and head and neck (adjusted HR 1.414; 95% CI, 1.112-1.798; $p < 0.001$) cancers. However, the risks for cervix uteri, bladder, lung, stomach, gall bladder, and melanoma cancers were not high in the HSCT group (Table 5). Notably, a lower risk of prostate and liver cancer in the HSCT group was found (adjusted HR 0.725; 95% CI, 0.57-0.921; $p < 0.001$ and adjusted HR 0.193; 95% CI, 0.152-0.245; $p < 0.001$, respectively).

DISCUSSION

This nationwide population-based cohort study demonstrated that HSCT recipients were related to a significantly high risk of developing malignant neoplasms ($p = 0.017$). Furthermore, HSCT recipients possessing the highest adjusted HR of secondary malignancies were observed in the hospital center group. The complexity of comorbidity and advanced screening tools in hospital centers was assumed to lead to an overall higher cumulative risk of secondary malignancy during the follow-up. In this study, the median follow-up duration was 2.21 (maximum 10.65) years, 2.16 years for HSCT recipients (maximum 10.53 years), and 2.57 years for the control cohort (maximum 10.65 years). A Japanese population-based study in 2018 involving 31,867 HSCT recipients (21,189 allogeneic and 10,678 autologous HSCTs) revealed a median follow-up duration of 2.6 years among transplantation survivors.[6] By contrast, a European retrospective study of 364 CBSCT recipients and 3,329 irrelevant donors revealed a median follow-up duration of 6.0 years.[7] Pediatric populations (aged <18 years

TABLE 3. Cancer Factors Stratified by Variables Listed in the Table Using Cox Regression.

	With HSCT			Without HSCT			With vs. without (reference)			
Stratified	Events	PYs	Rate (per 105 PYs)	Events	PYs	Rate (per 10^5 PYs)	Adjusted HR	95% CI	95% CI	p
Total	106	15,634.70	677.98	294	66,085.33	444.88	1.348	1.055	1.721	0.017
Sex										
Male	61	8,812.21	692.22	159	36,220.04	438.98	1.395	1.092	1.781	0.009
Female	45	6,822.49	659.58	135	29,865.29	452.03	1.291	1.010	1.648	0.042
Level of care										
Hospital center	78	10,545.45	739.66	99	20,939.15	472.80	1.475	1.160	1.876	<0.001
Regional hospital	19	4,033.76	471.02	106	31,045.74	341.43	1.301	1.023	1.654	0.033
Local hospital	9	1,055.49	852.68	89	14,100.45	631.19	1.274	1.002	1.620	0.048

Adjusted HR, adjusted hazard ratio: adjusted for the age, sex, comorbidity, and level of care; CI, confidence interval; competing risk variable, all-cause mortality; PYs, person-years

TABLE 4. Factors of Secondary Malignancy Stratified by Variables Listed in the Table Using Cox Regression.

HSCT subgroup	Populations	Events	PYs	Rate (per 10^5 PYs)	Adjusted HR	95% CI	95% CI	p
Without HSCT	12,236	294	66,085.33	444.88	Reference			
With HSCT	3,059	106	15,634.70	677.98	1.348	1.055	1.721	0.017
Autologous HSCT	1,378	60	7,426.95	807.87	1.533	1.148	2.046	0.004
Allogeneic HSCT	1,641	44	7,986.89	550.90	1.286	0.920	1.797	0.141
CBSCT	40	2	220.86	905.56	3.472	0.857	14.064	0.081
HSCT without total body irradiation	2,533	91	13,158.21	691.58	1.577	0.924	2.693	0.095
HSCT, with total body irradiation	526	15	2,476.50	605.69	1.419	1.104	1.823	0.006

Adjusted HR, adjusted hazard ratio: adjusted for sex, comorbidity, and level of care; CBSCT, cord blood stem cell transplantation; CI, confidence interval; GVHD, graft-versus-host disease; PYs, person-years

at the time of transplantation) were excluded from this study. The longer follow-up duration was due to the possibility of delayed engraftment associated with CBSCT recipients.[7] Our study included 40 CBSCT recipients, which constituted a small proportion of the study group. Therefore, the median follow-up duration in this study should be sufficient.

Association between secondary malignancies and HSCT has been documented in previous studies.[8-12] In 2009, an American population-based cohort study of 28,874 allogeneic HSCT recipients showed a two-fold risk of subsequent solid cancers compared with the general population.[4] In Asia, a 2014 Japanese population-based cohort study of 17,545 allogeneic HSCT recipients revealed a standardized incidence ratio (SIR) of 1.8 for developing secondary malignancies compared with the Japanese general population.[13] In 2011, a single-center retrospective study of 170 allogeneic HSCT recipients in Taiwan showed a 10-year cumulative incidence of subsequent malignancies of 2.89%.[14] However, large population-based studies concerning secondary cancers post-HSCT in Taiwan are lacking.

Among secondary malignancies in HSCT recipients, this study revealed a significant risk of secondary bone (adjusted HR 27,899), laryngeal (adjusted HR 6,643), kidney (adjusted HR 5,580), corpus uteri (adjusted HR 3,986), esophageal, pancreatic, thyroid (adjusted HR 1,993), skin (adjusted HR 1,992), colorectal (adjusted HR 1,724) female breast (adjusted HR 1.55), and head and neck (adjusted HR 1.414) cancers. Similarly, a nationwide retrospective study conducted in the USA reported that the malignancy risk of the bone, buccal cavity, and thyroid in 19,229 allogeneic or syngeneic transplant recipients was significantly high, with an observed/expected ratio of 13.4, 11.1, and 6.6, respectively.[8] In 2019, a European population-based cohort study of 220,617 HSCT recipients disclosed the five most frequent secondary malignancies as lung, breast, colorectal, and prostate cancer, and skin melanoma.[15]

In Asia, a Japanese population-based, retrospective cohort study demonstrated a significantly higher risk of oral cavity (SIR 15.7), upper gastrointestinal (SIR 8.5), skin (SIR 7.2), brain (SIR 4.1), and lower gastrointestinal (SIR 1.9) cancers in HSCT recipients.[13] As opposed to previous studies in the UK and USA (8, 15), higher

TABLE 5. Sensitivity Test for Factors of Cancer Types Using Cox Regression.

	With HSCT			Without HSCT			With vs without (reference)				
Cancer type	Events	PYs	Rate (per 10^5 PYs)	Events	PYs	Rate (per 10^5 PYs)	Ratio	Adjusted HR	95% CI	95% CI	p
Overall	106	15,634.70	677.98	294	66,085.33	444.88	1.523	1.348	1.055	1.721	0.017
Melanoma	0	15,634.70	0.00	3	66,085.33	4.54	0	0.000	-	-	0.999
Skin	2	15,634.70	12.79	4	66,085.33	6.05	2.114	1.992	1.565	2.531	<0.001
Kaposi's sarcoma	0	15,634.70	0.00	0	66,085.33	0.00	0	-	-	-	-
Head and neck	11	15,634.70	70.36	31	66,085.33	46.91	1.500	1.414	1.112	1.798	0.004
Esophagus	4	15,634.70	25.58	8	66,085.33	12.11	2.112	1.993	1.567	2.534	<0.001
Stomach	2	15,634.70	12.79	9	66,085.33	13.62	0.939	0.886	0.696	1.126	0.384
Colorectal	16	15,634.70	102.34	37	66,085.33	55.99	1.828	1.724	1.355	2.191	<0.001
Liver	3	15,634.70	19.19	62	66,085.33	93.82	0.205	0.193	0.152	0.245	<0.001
Gall bladder	1	15,634.70	6.40	5	66,085.33	7.57	0.845	0.797	0.627	1.013	0.062
Pancreas	2	15,634.70	12.79	4	66,085.33	6.05	2.114	1.993	1.567	2.534	<0.001
Larynx	5	15,634.70	31.98	3	66,085.33	4.54	7.044	6.643	5.224	8.446	<0.001
Lung	9	15,634.70	57.56	39	66,085.33	59.01	0.975	0.920	0.723	1.169	0.297
Bone	7	15,634.70	44.77	1	66,085.33	1.51	29.65	27.899	21.939	35.471	<0.001
Female breast	14	15,634.70	89.54	36	66,085.33	54.48	1.644	1.550	1.219	1.971	<0.001
Male breast	0	15,634.70	0.00	0	66,085.33	0.00	-	-	-	-	-
Uterus	1	15,634.70	6.40	0	66,085.33	0.00	-	∞	-	-	0.999
Cervix uteri	2	15,634.70	12.79	6	66,085.33	9.08	1.409	1.329	1.045	1.689	0.022
Corpus uteri	1	15,634.70	6.40	1	66,085.33	1.51	4.238	3.986	3.134	5.067	<0.001
Prostate	2	15,634.70	12.79	11	66,085.33	16.65	0.768	0.725	0.570	0.921	<0.001
Bladder	3	15,634.70	19.19	11	66,085.33	16.65	1.153	1.087	0.855	1.382	0.189
Kidney	7	15,634.70	44.77	5	66,085.33	7.57	5.914	5.580	4.388	7.094	<0.001
Thyroid	4	15,634.70	25.58	8	66,085.33	12.11	2.112	1.993	1.567	2.534	<0.001
Unspecified	10	15,634.70	63.96	10	66,085.33	15.13	4.227	3.986	3.134	5.067	<0.001

Adjusted HR, adjusted hazard ratio; CI, confidence interval; PYs, person-years

risks of melanoma and lung and prostate cancer were not found in the present study. Instead, a lower risk of prostate cancer was noted in HSCT recipients ($p < 0.001$).

Rizzo et al.[4] reported SIRs of melanoma and skin cancers of 3.5 and 4.2, respectively, among 28,874 HSCT recipients in an American population-based cohort study. A Danish population-based cohort study of 1,007 allogeneic HSCT recipients revealed a significant risk of cutaneous squamous cell carcinoma (SCC), melanoma, and basal cell carcinoma (BCC), with HRs of 18.3, 5.5, and 3.1, respectively.[16] However, the risk of skin cancer was not increased in autologous HSCT recipients.[16] In Asia, a Japanese retrospective population-based study of 17,545 allogeneic HSCT recipients showed a significantly high risk of skin cancers (SIR 7.2) without distinguishing cancer subtypes.[13] Consistently, our study showed a high risk of skin cancers after HSCT ($p < 0.001$), excluding melanoma ($p = 0.999$). The advanced Fitzpatrick skin type (FST) of Taiwanese (types III and IV) compared with that of Caucasians possibly explained the insignificant risk of melanoma found in the present study because FST has been delineated as an independent risk factor for cutaneous SCC development among organ-transplant recipients.[17] Risk factors for secondary skin cancer included chronic GVHD, earlier age at the time of HSCT, and myeloablative TBI.[4,8,13,18-20] A period of lymphocytopenia and cell-mediated immunodeficiency occurring after both autologous and allogeneic HSCTs has been postulated to hinder the inhibition of malignant transformation of precursor skin lesions.

Several large-scale studies have reported high risks of subsequent malignancies after autologous[2,21] or allogeneic[4,9,13,19] HSCT. Our study also showed a significant risk of secondary malignancies in both autologous and allogeneic HSCT recipients, with adjusted HRs of 1.733 ($p < 0.001$) and 1.438 ($p = 0.033$, respectively, but not in CBSCT (two events in 40 recipients, $p = 0.076$)m. Despite few comparative data about secondary malignancy risk between allogeneic and autologous transplantations, a European retrospective, population-based study of 68,936 recipients revealed no significant difference in incident risk of thyroid cancer between allogeneic and autologous transplantations ($p = 0.745$).[22] Compared with SCT from haploidentical donors, umbilical cord blood transplantation was associated with a higher tendency for acute GVHD,[23] whereas secondary malignancy was usually associated with chronic GVHD.[8,13] Allogeneic HSCT recipients are particularly vulnerable to GVHD, an inflammatory circumstance caused by donor T cells invading host tissues.[24] Immunosuppressants are needed to alleviate chronic GVHD.[25] Although not developing GVHD and thus being less immunosuppressive with autologous HSCT, compromised immune system may persist for 1 year.[26]

We observed a high risk of cancers in both male and female patients, with an adjusted HR of 1.487 and 1.376, respectively. An Australian population-based cohort study of 717 pediatric (< 15 years) allogeneic HSCT recipients also revealed a high risk of subsequent malignancies in both men and women with SIRs of 21.0 and 19.2, respectively,[27] whereas a high cancer risk was noted only in men in another Australian population-based cohort study of 3,273 adult allogeneic HSCT recipients (aged >15 years).[28] Sex may also contribute to the variable prevalence of different cutaneous malignancies. A greater risk for cutaneous SCC and oral cavity was reported in male recipients,[4,8] whereas a high risk of melanoma was noted in female recipients.[4] Although why male patients had an excess risk of cutaneous SCC was unclear, the cumulative effect of ionizing radiation, immunosuppression, and other variable risk factors are more common among men than women.[8] Apart from melanoma, women have been reported to have a high incidence of thyroid (RR 2.9) and breast[29,30] cancers.

Several factors contribute to the etiopathogenesis of secondary malignancies after SCT. In 1997, a US nationwide retrospective study of 19,229 allogeneic or syngeneic transplant recipients revealed a high risk of new solid malignancies with higher TBI doses.[8] The present study disclosed a high risk of secondary malignancies in HSCT with TBI (adjusted HR 1.419, $p = 0.006$). TBI-based condition or radiation exposure has been reported as the paramount risk factor for solid cancers.[4,31] Undergoing radiotherapy at a young age (< 30 years) and receiving a higher dosage increase the risk of malignancies.[32] Genetic factors may also play a role because the application of human leukocyte antigen-mismatched donors has been associated with subsequent malignant neoplasms.[4,8,33,34]

Study Limitations

The method of a fourfold propensity score matching for sex, age, comorbidities, and level of care between the HSCT group and control groups provided sufficient statistical power to evaluate the relationship between HSCT and subsequent malignancies. Nonetheless, this study had several limitations. First, this study did not include patients aged <18 years. Second, only a few events and CBSCT recipients were analyzed (2 events in 40 recipients). Third, we did not evaluate acute and chronic GVHD as risk factors in the subgroup analysis, and the individual incident risk of cutaneous SCC and BCC was not estimated. Fourth, as incomplete information was obtained from the NHIRD, we could not clarify pre-HSCT therapies, HSCT conditioning, or risk factors that play possible roles in oncogenesis, such as genetic factors, tobacco history, and ultraviolet light exposure history in our within-cohort analyses. Information on the tumor stage upon diagnosis, lesion sites, and treatment details are lacking. Finally, our study population comprised mostly Chinese individuals. Therefore, the extrapolation of our results to other ethnicities may lead to a certain bias. Further comprehensive studies with long-term follow-up are required to address the aforementioned issues.

Our study demonstrated that in Taiwan, HSCT recipients have a 1.348-fold higher risk of secondary malignancies. The cancer subgroup analysis disclosed that the three cancers with the highest risks were bone (adjusted HR, 27.899, $p < 0.001$), laryngeal (adjusted HR, 6.643, $p < 0.001$), and kidney (adjusted HR, 5.580, $p < 0.001$) cancers. Both sexes, patients treated at hospital centers, along with HSCT with TBI, were found to have a high risk of secondary cancers. Physicians should notify recipients about the lifelong risk of secondary cancers and emphasize the necessity of regular follow-up for early cancer or precursor lesion detection.

Carcinogenic exposures (e.g.,., ultraviolet radiation, alcohol, and tobacco) should be also avoided.

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Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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