OPEN

Cancer After Pediatric Kidney Transplantation: A Long-term Single-center Experience in Japan

Tomoo Yabuuchi, MD,[1] Kenichiro Miura, MD, PhD,[1] Satoru Shimizu, PhD,[2] Naoto Kaneko, MD,[1] Kiyonobu Ishizuka, MD,[1] Shoichiro Kanda, MD, PhD,[3] Hiroko Chikamoto, MD, PhD,[1] Yuko Akioka, MD, PhD,[1,4] Mikiya Fujieda, MD, PhD,[5] and Motoshi Hattori, MD, PhD[1]

Background. The cancer incidence, types, and risk factors after pediatric kidney transplantation (KT) have been reported in the United States, Canada, Europe, Australia, and New Zealand. However, no information is available about cancer in pediatric KT recipients in Asian countries. **Methods.** Children aged <20 y who underwent initial KT from 1983 to 2016 were analyzed. We compared the cancer incidence with that in the general Japanese population using standardized incidence ratio and examined posttransplant cancer risk using Cox proportional hazards models. **Results.** A total of 356 children (median age, 11.7 y; interquartile range, 5.0–17.6) received KT with a follow-up period of 4466 person-years. The median age of cancer onset was 18.5 y (interquartile range, 8.0–32.3), and 13 cancers occurred in 12 patients (3.4%). Two patients died from cancer. The most common cancers were posttransplant lymphoproliferative disorders (PTLDs) (38.5%). The median time to PTLD and non-PTLD diagnosis after KT was 0.6 and 16.4 y, respectively. There was no occurrence of skin cancer. The posttransplant cancer incidence was 9.9 times higher than that in the general age-matched population (standardized incidence ratio = 9.9; 95% confidence interval, 4.80-18.39). The cumulative cancer incidence was 5.3% in 20 y after KT, which is lower than that reported in previous studies. We could not identify any risk factors for all cancer after KT in all patients, whereas subgroup analysis in 264 patients with available data of recipient Epstein-Barr virus serological status showed that recipient Epstein-Barr virus-negative serology was an independent risk factor for cancer development. **Conclusions.** The incidence of cancer is higher in Japanese pediatric KT recipients than in the general population. The cumulative incidence of cancer after KT was lower in our population than that previously reported. This may be because there was no skin cancer observed in the Japanese pediatric KT recipients in our study.

(*Transplantation Direct* 2021;7: e687; doi: 10.1097/TXD.0000000000001137. Published online 22 March, 2021.)

INTRODUCTION

Kidney transplantation (KT) is an optimal treatment in children, with significant benefits of improving life prognosis and quality and improving physical and psychomotor development.[1] In recent years, with enhanced surgical techniques, more potent immunosuppressive medications, greater understanding of pediatric-specific pharmacokinetics, and use of evidence-based medication protocols, kidney allograft survival has significantly improved.[2] Patients can live for more than several decades after pediatric KT, so it is important to understand the effects that may influence long-term prognosis after pediatric KT.

Received 19 January 2021.

Accepted 21 January 2021.

[1] Department of Pediatric Nephrology, Tokyo Women's Medical University, Tokyo, Japan.

[2] Medical Research Institute, Tokyo Women's Medical University, Tokyo, Japan.

[3] Department of Pediatrics, The University of Tokyo, Tokyo, Japan.

[4] Department of Pediatrics, Saitama Medical University, Saitama, Japan.

[5] Department of Pediatrics, Kochi Medical School, Kochi University, Kochi, Japan.

This work was supported by a Grant-in-Aid for Scientific Research (C) (JP18K07830 to K.M., and JP18K07857 to M.H., and JP20K08237 to T.Y.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

The authors declare no conflicts of interest.

T.Y. participated in study design, data collection, data analysis and interpretation, drafting the article, and final approval of the version to be published. K.M. participated in study design, data collection, data analysis and interpretation, drafting the article, and critical revision of the article. S.S. participated in data analysis and interpretation. N.K. and K.I. participated in data collection. S.K., H.C., and Y.A. participated in data collection and critical revision of the article. M.F. performed quantification of EBV viral load. M.H. participated in study design, data collection, data analysis and interpretation, drafting the article, and final approval of the version to be published.

T.Y. and K.M. contributed equally to this article.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

Correspondence: Motoshi Hattori, MD, PhD, Department of Pediatric Nephrology, Tokyo Women's Medical University, School of Medicine, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. (hattori@twmu.ac.jp).

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001137

Cancer is an important complication after KT in both adults and children.[3,4] Some reports describing the incidence and types of cancer and risk factors for cancer after pediatric KT have been published from the United States, Canada, Europe, Australia, and New Zealand.[5-10] However, to date, cancer after KT has not been studied in Asian children.

The aim of this study was to examine the incidence and the types of cancer and risk factors for cancer after pediatric KT at a single center in Japan.

MATERIALS AND METHODS

Patients

The study included children under 20 y of age who received their first KT at the Department of Pediatric Nephrology, Tokyo Women's Medical University during 34 y from January 1983 to December 2016. After obtaining approval from our ethics committee (Tokyo Women's Medical University Ethical Review Board approval number, 3693), the medical records were reviewed retrospectively. This study was conducted in accordance with the principles of the Declarations of Helsinki and Istanbul. The requirement for written informed consent was waived because of the retrospective nature of the study.

Data Collection

The covariates analyzed were recipient characteristics (age, sex, race, cause of end-stage kidney disease [ESKD], pretransplant immunosuppressant use, pretransplant dialysis period, cytomegalovirus [CMV] serological status, Epstein-Barr virus [EBV] serological status, cancer onset date, and cancer type), donor characteristics (age and donor type [living or deceased]), transplant characteristics (transplant y, preemptive KT, ABO blood type compatibility, HLA mismatch, induction agents, baseline immunosuppressants, and the use of rituximab), and transplant outcomes (graft loss and death). Graft loss was defined as the return to dialysis or retransplant, excluding death with a functioning graft. The patients were censored at the date of death, date of last contact, or December 31, 2016, whichever came first, irrespective of occurrence of graft loss.

Cancer

Cancer was included in the analysis if it was diagnosed after transplantation, and benign tumors and carcinoma in situ were excluded, as previously reported.[9,10] We extracted information directly from the medical record. The recipients in our hospital were closely followed up and regularly asked to provide an updated medical and psychosocial history, including development of new comorbidities and cancers including skin cancer. Pretransplant cancers were also identified using the medical record.

Immunosuppression Protocols

Our immunosuppressive protocols have been described previously.[11-18] In brief, immunosuppressive protocols were stratified according to 2 different time periods at our institution. Between 1983 and 2001, a protocol using methylprednisolone, azathioprine or mizoribine, and cyclosporine or tacrolimus was used.[11,12] Cyclosporine was used from 1983, and tacrolimus was used from 1997. From 2002, mycophenolate mofetil (MMF) and basiliximab were introduced. At our institution, a protocol using basiliximab, cyclosporine or tacrolimus, MMF, and methylprednisolone was used.[13]

ABO-incompatible KT has been performed since 1989. Cyclosporine or tacrolimus, azathioprine, methylprednisolone, antilymphocyte globulin, deoxyspergualin, and local graft irradiation were used as standard immunosuppressive agents between 1989 and 2001 at our institution.[14,15] Prophylactic deoxyspergualin (5 mg/kg body weight per d) was administered intravenously during the first 5 d of the cyclosporine regimen, but not with the tacrolimus regimen for fear of over immunosuppression.[15] Antilymphocyte globulin (500 mg/m^2/d) was administered for 2 wk.[15] All patients underwent preoperative plasmapheresis (PP) or immunoadsorption to reduce anti-blood type antibody titers to <1:16.[15] A splenectomy was performed at the time of transplantation until 2005.[16] For preconditioning therapies for ABO-incompatible KT recipients, use of calcineurin inhibitors, MMF, and methylprednisolone was initiated 1–2 wk before transplantation.[16] PP was performed 7–10 d before transplantation to reduce the titers to <1:8–1:16.[16] We have used rituximab as a substitute for splenectomy in ABO-incompatible KT since 2005.[16] One dose of rituximab (150–375 mg/m^2) is administered 2–3 wk before transplantation.[16]

In patients with focal segmental glomerulosclerosis, we introduced prophylactic PP in 1991.[17] In the period from 1991 to 2007, patients who underwent living-related donor transplantation received 2–3 sessions of prophylactic PP in the 7 d before transplantation.[17] Since 2008, a single dose of rituximab (375 mg/m^2, max 500 mg) along with immunosuppression of methylprednisolone (1 mg/kg/d, max 20 mg), tacrolimus (target trough level: 8–12 ng/mL), and MMF (600 mg/m^2/d) were started 14–21 d before living-related donor transplantation.[18] Four sessions of PP were also performed on pretransplantation days −12, −10, −7, and −5.[18]

EBV and CMV Serology

Recipient CMV serology testing was performed for all cases in the study period, and EBV serology testing was performed for all cases since 2000. CMV IgG antibody was measured by fluorescent antibody or enzyme immunoassay methods. For EBV, virus capsid antigen or EBV nuclear antigen antibodies were measured by fluorescent antibody or enzyme immunoassay methods.[19]

EBV Monitoring

Since 2006, the EBV monitoring protocol consisted of monthly measurements of EBV viral load and antibody in peripheral blood during the first 3 mo after grafting, and every 1–3 mo thereafter.[20] Additional samples were obtained if necessary. EBV viral load was quantified in peripheral blood mononuclear cells. The immunosuppressive therapy was stopped or reduced following the modified guidelines of the Southwest Oncology Group and the Eastern Cooperative Oncology Group for cases with posttransplant lymphoproliferative disorder (PTLD).[21] MMF was discontinued when EBV loads of >1000 copies/μg DNA persisted for over 6 mo, and tacrolimus and cyclosporine were further reduced or stopped when the EBV load increased to >10 000 copies/μg DNA even in the absence of EBV-associated symptoms.[20]

CMV Monitoring

No patients had antiviral prophylaxis, but regular tests for CMV antigenemia were performed. If CMV antigenemia or CMV infection appeared, ganciclovir was administered until the test for CMV antigenemia was negative.[20]

Cancer Prevention Measures in KT of Wilms' Tumor 1-related Syndrome Cases

Since 2000, bilateral native nephrectomy was performed before or at the same time as KT in patients with Wilms' tumor 1-related syndrome.[22] Because of the high risk of gonadal tumor, gonadectomy was performed as needed for patients with Frasier syndrome.[23]

Statistical Analysis

Results are expressed as frequencies (percentages) or the median (interquartile range [IQR]). Person-years for the observed were counted from the time of transplantation to the time of death, loss to follow-up, or end of study (December 31, 2016), whichever came first. For cancer patients, the follow-up period is from the time of transplantation to the first cancer diagnosis, and for cancer-free cases, the follow-up period is from the time of transplantation to death, follow-up interruption, or the end of the study. Survival analyses were estimated using the Kaplan-Meier method. Standardized incidence ratio (SIR) was calculated as the number of observed cancer cases among KT recipients divided by the expected number of cancer cases. The expected number of cancer cases was obtained from the product of national age-specific, sex-specific incidence rates obtained from the Japan National Cancer Registry[24] and the number of person-years at risk. The SIR 95% confidence intervals (CIs) were calculated by assuming that the observed cancers follow a Poisson distribution. Univariable and multivariable Cox proportional hazard models assessed the risk factors for cancer development after transplantation. EBV status was excluded from the covariates because it was limited to 264 cases. Also, rituximab was excluded because no patients administered rituximab developed cancers. Variables that had an association with cancer incidence at $P < 0.2$ in the unadjusted analyses were included in the multivariable-adjusted analyses. Additionally, a subgroup analysis was performed in 264 patients with available data of recipient EBV serological status. Donor age, ABO compatibility, antilymphoblast globulin, and baseline immunosuppression were excluded from the analysis because there were no occurrences of cancer in subgroups stratified by these covariates. The transplant eras 1983–1996 and 1997–2006 were combined, because there were only 2 patients with available data of recipient EBV serological status in the 1983–1996 group. Statistical analysis using JMP Pro 14.0 (SAS Institute, Cary, NC) and R version 3.4.2 (R Foundation for Statistical Computing) was performed for all statistical analyses. $P < 0.05$ was considered statistically significant.

RESULTS

Cohort Description

A total of 356 children underwent their first KT between 1983 and 2016. These patients visited our hospital from all over the country, mainly the Tokyo area. The median follow-up period from transplantation was 11.7 y (IQR, 5.0–17.6) and the total observation period was 4466 person-years. There were 112 patients who were lost to follow-up. Of these, 79 had functioning graft and 33 had returned to dialysis at their last follow-up. Table 1 shows the patient characteristics. The median age at transplantation was 12.0 y (IQR, 8.1–15.6). All patients but 1 were Japanese. Congenital anomalies of the kidney and urinary tract (CAKUT) were the most common primary disease, accounting for 152 (42.7%) cases. Pretransplant immunosuppression for nephritis or nephrotic syndrome was used in 95 (26.7%) patients. Sixty-nine of 264 (26.1%) patients evaluated

TABLE 1.

Characteristics of pediatric kidney transplant recipients

Variable		n (%)
Recipient characteristics		
Age at transplantation (y)	0–4	31 (8.7)
	5–9	97 (27.2)
	10–14	121 (34.0)
	15–19	107 (30.1)
Sex	Male	214 (60.1)
Race	Japanese	355 (99.7)
Cause of ESKD	CAKUT	152 (42.7)
	FSGS	59 (16.6)
	Glomerulonephritis	66 (18.5)
	Other/unknown	79 (22.2)
Pretransplant immunosuppression for nephritis or NS		95 (26.7)
EBV-negative serology[a]		69 (26.1)
CMV-negative serology		166 (46.6)
Duration of dialysis before KT (y)	0–3	246 (69.1)
	4–12	110 (30.9)
PEKT		62 (17.4)
Donor characteristics		
Donor type	Living donor	299 (84.0)
Donor age[b]	>42 y	177 (50.0)
Transplant characteristics		
Transplant era	1983–1996	96 (27.0)
	1997–2006	132 (37.1)
	2007–2016	128 (36.0)
ABO type	Compatible	328 (92.1)
	Incompatible	28 (7.9)
HLA mismatch[c]	0–2	98 (27.8)
	3–6	254 (72.2)
Induction agent	Basiliximab	193 (54.2)
	Antilymphocyte globulin	9 (2.5)
Baseline immunosuppression	Tacrolimus/MMF/methylprednisolone	138 (38.8)
	Cyclosporin/MMF/methylprednisolone	66 (18.5)
	Tacrolimus/AZA/methylprednisolone	14 (3.9)
	Cyclosporin/AZA/methylprednisolone	49 (13.8)
	Tacrolimus/MZ/methylprednisolone	37 (10.4)
	Cyclosporin/MZ/methylprednisolone	43 (12.1)
	Other regimen	9 (2.5)
Use of rituximab		34 (9.6)
Transplant outcomes		
Graft loss		97 (27.2)
Death		12 (3.4)

[a]Missing data for 92.
[b]Missing data for 2.
[c]Missing data for 4.
AZA, azathioprine; CAKUT, congenital anomalies of the kidney and urinary tract; CMV, cytomegalovirus; EBV, Epstein-Barr virus; ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; KT, kidney transplantation; MMF, mycophenolate mofetil; MZ, mizoribine; NS, nephrotic syndrome; PEKT, preemptive kidney transplantation.

were seronegative for EBV, and 166 of all 356 (46.6%) patients were seronegative for CMV. The median duration of dialysis was 1.8 y (IQR, 0.5–3.5). Preemptive KT was performed in 62 cases (17.4%). Living KT was performed in 299 cases (84.0%). ABO-incompatible transplantation was performed in 28 patients (7.9%). The median number of HLA mismatches was 3 (IQR, 2–3). There were 97 graft losses (27.2%) and 12 deaths (3.4%) during the observation period. Two of the patients died from cancer with functioning grafts.

Incidence and Types of Cancer

Table 2 shows the types of cancers in the KT recipients. The median age at diagnosis for all cancers was 18.5 y (IQR, 8.0–32.3), and the time to cancer diagnosis after transplantation was 8.7 y (IQR, 0.8–18.5). The age at diagnosis of PTLD was 11.5 y (IQR, 6.2–22.4), and the time to PTLD diagnosis after transplantation was 0.6 y (IQR, 0.4–6.6). The age at diagnosis of non-PTLD cancers was 31.7 y (IQR, 17.0–38.6), and the time to cancer diagnosis after transplantation was 16.4 y (IQR, 5.4–27.2) (Table 2). EBV-associated PTLD did not occur in patients who underwent KT after 2006. There was no occurrence of Wilms' tumor in 7 patients with Wilms' tumor 1-related syndrome who underwent KT after 2000. A total of 13 cancers developed in 12 patients (3.4%). The most common cancer was PTLD (n = 5, 38.5%). Among patients with PTLD, 4 cases were EBV-associated PTLD and 1 case was non-EBV-associated PTLD. Renal cell carcinoma and lung cancer were documented in 2 patients each (15.4%). Brain tumor, breast cancer, thyroid cancer, and Wilms' tumor were documented in 1 patient each (7.7%) (Table 2). There was no recurrence of cancer in 4 patients with pretransplant cancer. There was no second de novo malignancy. The cumulative incidence of all cancers was 1.5%, 1.9%, 5.3%, and 14.7% for 5, 10, 20, and 30 y, respectively (Figure 1). The cumulative incidence of PTLD was 0.6%, 0.9%, 1.2%, and 1.2% for 6, 12, 18, and 24 mo, respectively. In contrast, the cumulative incidence of non-PTLD cancers was 0.3%, 0.7%, 3.6%, and 13.1% for 5, 10, 20, and 30 y, respectively (Figure 1).

Outcomes of Patients Who Underwent EBV Polymerase Chain Reaction Monitoring

There were 69 recipients with EBV-negative serology in our study, of which 40 were transplanted after 2007. Of these, 25 patients underwent EBV polymerase chain reaction (PCR) monitoring at our center. The remaining 15 patients were transferred to other hospitals within 3 mo after transplantation, and long-term results of EBV PCR monitoring were not available. Of the 25 patients who were followed up at our center, 15 became EBV PCR positive during follow-up. Of these, 4 cases had EBV DNA of ≥1000 copies/μgDNA in whole blood persisting for >6 mo, which required reduction of CNI or discontinuation of MMF. No patients were given mammalian target of rapamycin inhibitor. There were no occurrences of rejection and graft loss except for 1 patient, who had T cell–mediated rejection and graft loss due to nonadherence (Table S1, SDC, http://links.lww.com/TXD/A318).

Standardized Incidence Ratio

After a median follow-up time of 11.7 y, 13 incident cancers were observed in the transplanted population compared with the expected number of 1.3 (SIR = 9.93; 95% CI, 4.80-18.39).

Risk Factors for Cancer After KT

Risk factors for cancer after KT were examined using Cox regression. Table 3 shows the results of univariate analysis of cancer development after KT. The results of univariate analysis show that patients with EBV-negative serology were at a higher risk of developing cancer (hazard ratio, 8.48; 95% CI, 1.82-59.40). Variables with $P < 0.2$ (age at transplantation, cause of ESKD, and CMV serological status) were included in the multivariate analysis. EBV serological status was not included in the multivariate analysis because the data were limited to 264 patients. No independent risk factors for cancer development were identified, likely because of the small number of events (Table 4). Additionally, a subgroup analysis was performed in 264 patients with available data of recipient EBV serological status. Of these, 8 developed cancer (PTLD in 5 patients and renal cell carcinoma, breast cancer, and Wilms' tumor in each 1 patient). Table S2 (SDC, http://links.lww.com/TXD/A318) shows the results of univariate analysis of cancer

TABLE 2.

Characteristics of cancers after kidney transplantation

Cancer	n	Median (IQR)	
		Age at diagnosis (y)	Interval between transplant and diagnosis (y)
All cancer	13	18.5 (8.0–32.3)	8.7 (0.8–18.5)
PTLD	5	11.5 (6.2–22.4)	0.6 (0.4–6.6)
Other	8	31.7 (17.0–38.6)	16.4 (5.4–27.2)
Renal cell carcinoma	2	20.1–45.5	5.4–27.2
Lung cancer	2	31.7–45.5	19.2–27.2
Brain tumor	1	17	14.5
Breast cancer	1	38.6	29.2
Thyroid cancer	1	32.5	16.4
Wilms' tumor	1	3.8	1.2

IQR, interquartile range; PTLD, posttransplant lymphoproliferative disease.

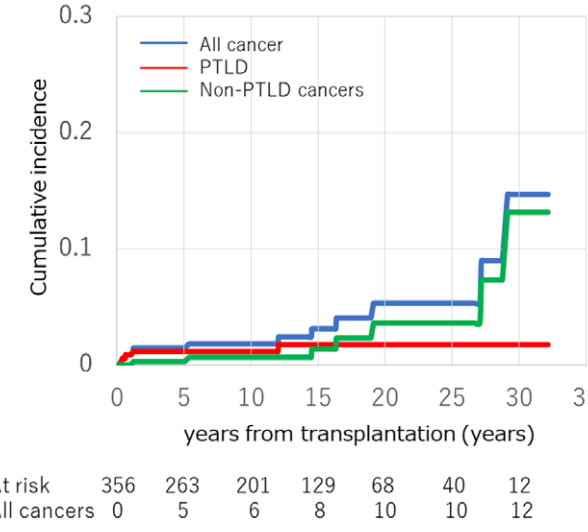

FIGURE 1. Cumulative incidence of cancer in kidney transplant recipients. The cumulative incidence of cancer was 1.5%, 1.9%, 5.3%, and 14.7% for 5, 10, 20, and 30 y, respectively. The cumulative incidence of PTLDs was 0.6%, 0.9%, 1.2%, and 1.2% for 6, 12, 18, and 24 mo, respectively, and did not increase thereafter. The cumulative incidence of other cancers was 0.3%, 0.7%, 3.6%, and 13.1% for 5, 10, 20, and 30 y, respectively. PTLD, posttransplant lymphoproliferative disorder.

TABLE 3.

Risk factors for cancer in pediatric kidney transplant recipients (univariate analysis)

Variable		HR (95% CI)	*P*
Recipient characteristics			
Age at transplantation (y)	0–4	Reference	
	5–9	0.29 (0.04-1.73)	0.166
	10–14	0.28 (0.05-1.50)	0.128
	15–19	0.53 (0.12-2.71)	0.417
Sex	Male	Reference	
	Female	0.92 (0.29-2.93)	0.893
Cause of ESKD	CAKUT	Reference	
	FSGS	2.98 (0.55-16.32)	0.195
	Glomerulonephritis	1.98 (0.42-10.36)	0.379
	Other/unknown	1.19 (0.16-7.2)	0.852
Pretransplant immunosuppression for nephritis or NS		1.06 (0.23-3.56)	0.935
EBV status (n = 264)	Recipient seropositive	Reference	
	Recipient seronegative	8.48 (1.82-59.40)	0.0065
CMV status	Recipient seropositive	Reference	
	Recipient seronegative	2.30 (0.72-8.62)	0.162
Duration of dialysis before KT (y)	0–2	Reference	
	3–12	0.76 (0.17-2.55)	0.672
PEKT		0.63 (0.03-3.35)	0.646
Donor characteristics			
Living donor		0.88 (0.23-5.74)	0.870
Donor age (y) (n = 354)	0–49	Reference	
	50–75	0.70 (0.04-3.79)	0.727
Transplant characteristics			
Transplant era	1983–1996	Reference	
	1997–2006	1.57 (0.38-7.26)	0.536
	2007–2016	0.58 (0.03-5.20)	0.645
ABO compatibility	Compatible	Reference	
	Incompatible	1.35 (0.07-7.20)	0.785
HLA mismatch (n = 352)	0–2	Reference	
	3–6	0.71 (0.22-2.67)	0.584
Induction agent	Basiliximab	1.64 (0.34-8.82)	0.532
	Antilymphoblast globulin	2.60 (0.14-14.19)	0.427
Baseline immunosuppression[a] (n = 347)	Tacrolimus/MMF/methylprednisolone	Reference	
	Cyclosporin/MMF/methylprednisolone	2.22 (0.31-15.84)	0.431
	Tacrolimus/AZA/methylprednisolone	1.75 (0.14-22.25)	0.677
	Cyclosporin/AZA/methylprednisolone	0.98 (0.12-8.23)	0.983
	Tacrolimus/MZ/methylprednisolone	1.92 (0.25-14.94)	0.536
	Cyclosporin/MZ/methylprednisolone	0.33 (0.02-4.85)	0.402
Functioning transplant		1.95 (0.55-8.01)	0.306

[a]Patients who were treated with the regimen consisting of methylprednisolone and cyclosporin or tacrolimus were excluded.

AZA, azathioprine; CAKUT, congenital anomalies of the kidney and urinary tract; CI, confidence interval; CMV, cytomegalovirus; EBV, Epstein-Barr virus; ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; HR, hazard ratio; KT, kidney transplantation; MMF, mycophenolate mofetil; MZ, mizoribine; NS, nephrotic syndrome; PEKT, preemptive kidney transplantation.

development after KT in these patients. Variables that had an association with cancer incidence at $P < 0.1$ in the unadjusted analyses (EBV serological status and cause of ESKD) were included in the multivariable-adjusted analyses. As a result, recipient EBV-negative serology was identified as an independent risk factor for cancer development (Table S3, SDC, http://links.lww.com/TXD/A318).

DISCUSSION

We examined cancer incidence after pediatric KT in a single-center cohort in Japan. Our patients were from all over the country, mainly the Tokyo area. According to the report of pediatric KT recipients in Japan, 2410 pediatric KTs were performed between 1983 and 2014, and CAKUT was the most common cause of ESKD (29.7%), followed by glomerulonephritis (16.3%) and FSGS (10.5%).[25] During the same period, 325 cases were transplanted at our institution, which accounted for 13.5% of all pediatric KT in Japan, and the cause of ESKD was similar. Twelve patients (3.4%) developed cancer during the median posttransplant follow-up period of 11.7 y. Pediatric KT patients were 9.9 times more likely to develop cancer than was the general population (SIR = 9.9; 95% CI, 4.80-18.39). This is not much different from previous reports indicating that the SIR for the development of nonskin cancers after childhood KT was 4.7–8.2.[8,9]

In this study, there was no incidence of skin cancer. This finding differs from reports from the United States, Europe, Australia, and New Zealand, all of which described skin cancer as the most common cancer after childhood KT.[8-10]

TABLE 4.

Risk factors for cancer in pediatric kidney transplant recipients (multivariable analysis)

Variable		HR (95% CI)	*P*
Age at transplantation (y)	0–4	Reference	
	5–9	0.30 (0.04-2.09)	0.221
	10–14	0.30 (0.05-1.77)	0.175
	15–19	0.52 (0.11-2.81)	0.427
Cause of ESKD	CAKUT	Reference	
	FSGS	3.01 (0.55-16.89)	0.188
	Glomerulonephritis	1.54 (0.29-8.60)	0.604
	Other/unknown	0.95 (0.12-5.98)	0.955
CMV status	Recipient seropositive	Reference	
	Recipient seronegative	2.01 (0.61-7.72)	0.256

CAKUT, congenital anomalies of the kidney and urinary tract; CI, confidence interval; CMV, cytomegalovirus; ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; HR, hazard ratio.

In addition to the use of immunosuppressants, UV exposure and human papillomavirus infection are related to skin cancer development.[26,27] The risk factors for skin cancer are low latitude, being Caucasian, and being of an increased age at the time of transplantation.[9] Most of the patients analyzed in the previous reports were Caucasian.[8-10] Studies in adults have shown that skin cancer is the most common cancer after KT in the United States, Europe, Australia, and New Zealand[28-30]; gastric and kidney cancers are common in Japan[31]; non-Hodgkin lymphoma is the most common cancer in Hong Kong[32]; and kidney and bladder cancer are the most common cancers in Taiwan.[33] It has been reported that colored races have a higher sun protection factor than Caucasians. Therefore, exposure to UV radiation may play a lesser role in heightening the risk for skin cancer in Asian.[34] These findings suggest that site-specific cancers after KT may differ greatly between Caucasian and Asian children just as they do in adults.

The cumulative cancer incidence after pediatric KT in this study was lower than that in previous reports, which detailed incidences of post-KT cancer of 3%–7% at 10 y, 7%–10% at 15 y, 13% at 20 y, and 23%–27% at 25 y.[5,8-10] The incidence of cancer in general pediatric population in East Asia has been reported to be lower than that in the North America, Europe, and Oceania,[35] which explains the reason for the low absolute risk of cancer in our study, despite comparable SIR to other studies. In previous reports, there were many skin cancer cases including nonmelanoma skin cancer and melanoma. The age-adjusted prevalence of melanoma is 33.6, 33.3, and 15.0 per 100 000 in Australia, New Zealand, and the United States, respectively.[36] Nonmelanoma skin cancer is not usually followed by cancer registries in those countries but is 18–20 times higher than the incidence of melanoma.[37] In contrast, the age-adjusted prevalence of skin cancer including melanoma is as low as 4.2 per 100 000 in Japan.[24] Thus, the absence of skin cancer may have contributed to the low cumulative incidence of cancer after KT in this study.

In this cohort, PTLD occurred in 5 patients at a median follow-up period of 0.6 y after transplantation and the median age at diagnosis was 11.5 y. Previous pediatric reports described that PTLD occurred at a median follow-up period of 3.0–6.6 y after KT and the median age at diagnosis was 14.2–18.0 y.[5,9] The time to onset of PTLD after pediatric organ transplantation is considered to be bimodal in the first year after transplantation and the third year after transplantation, and the former is considered to have more EBV-associated PTLD.[38] In this study, the observed PTLD was EBV-associated in 4 of 5 cases, which may have reduced the median period after transplantation.[5,9] PTLD is thought to occur in 2%–3% of pediatric KT recipients.[39] However, the incidence was 1.4% (5 of 356) in this study. In recent years, the incidence of EBV-associated PTLD has been decreasing because of proper use of immunosuppressants and regular monitoring of blood EBV levels as well as monitoring of CMV and BKV.[40] In our cohort, PTLD has not occurred in KT recipients since 2006, when we started regular monitoring of blood EBV levels. The risk of PTLD during years 1983–2006 (the period before EBV monitoring) was $5/(96+132)=0.022$. Thus, the expected number of PTLD from 2007 onward should be $128\times0.022=2.8$ cases, whereas we observed no occurrence of PTLD. The probability that none of these 128 KT recipients since 2007 developed PTLD is approximately $(1–0.022)^{128}=0.058$, which was a strong trend. Therefore, EBV PCR monitoring might have contributed to a low incidence of PTLD in our study. Reduction of immunosuppressive agents may enhance the risk of rejection and graft loss; however, such untoward effects did not occur in our patients. EBV PCR testing varies across institutions and the optimal testing modality (plasma or whole blood) and cutoff value to determine risk of PTLD are unknown. However, it has been reported that EBV DNA in peripheral blood mononuclear cells can increase weeks before the onset of PTLD symptoms,[41] which may have contributed to the low incidence of PTLD in this study. Optimal testing modality and cutoff value to determine risk of PTLD need to be established in future studies.

In this study, we could not identify any risk factors for developing cancer after pediatric KT because of the small number of events. In pediatric KT recipients, being Caucasian, older age at transplantation, having a functioning transplant, and living unrelated donors have all been reported as risk factors for developing cancer.[9,10] However, recipient EBV-negative serology was identified as a risk factor in 264 patients with available data of recipient EBV serological status. This finding is consistent with the observation that 5 of the 8 cancer cases had PTLD, because recipient EBV-negative serology is known to be a risk factor for the development of PTLD.[1-3] Risk factors for developing cancer after pediatric KT in Asia, including Japan, need to be examined in a larger cohort.

There are several limitations in the present study. This study is a single-center study with a limited patient population and number of cases. Limited data on donor EBV serology and CMV serology did not allow us to fully explore the relationship between EBV and CMV and the development of PTLD after KT. The effects of rejection and treatment, infections, and cumulative doses of immunosuppressive drugs on post-transplant cancer development have also not been examined in this study.

In conclusion, consistent with the results of previous studies, the incidence of cancer is higher in Japanese pediatric KT recipients than in the general population. The cumulative incidence of cancer after KT was lower than that in previous studies, which may be associated with the lack of skin cancer in the Japanese pediatric KT recipients included in this study.

ACKNOWLEDGMENTS

The authors thank Rebecca Porter, PhD, from Edanz Group (https://en-author-services.edanzgroup.com/ac) for editing a draft of this article.

REFERENCES

1. Holmberg C, Jalanko H. Long-term effects of paediatric kidney transplantation. *Nat Rev Nephrol.* 2016;12:301–311.
2. Dharnidharka VR, Fiorina P, Harmon WE. Kidney transplantation in children. *N Engl J Med.* 2014;371:549–558.
3. Mynarek M, Hussein K, Kreipe HH, et al. Malignancies after pediatric kidney transplantation: more than PTLD? *Pediatr Nephrol.* 2014;29:1517–1528.
4. Kitchlu A, Dixon S, Dirk JS, et al. Elevated risk of cancer after solid organ transplant in childhood: a population-based cohort study. *Transplantation.* 2019;103:588–596.
5. Koukourgianni F, Harambat J, Ranchin B, et al. Malignancy incidence after renal transplantation in children: a 20-year single-centre experience. *Nephrol Dial Transplant.* 2010;25:611–616.
6. Smith JM, Martz K, McDonald RA, et al. Solid tumors following kidney transplantation in children. *Pediatr Transplant.* 2013;17:726–730.
7. Smith JM, Martz K, Blydt-Hansen TD. Pediatric kidney transplant practice patterns and outcome benchmarks, 1987-2010: a report of the North American Pediatric Renal Trials and Collaborative Studies. *Pediatr Transplant.* 2013;17:149–157.
8. Ploos van Amstel S, Vogelzang JL, Starink MV, et al. Long-term risk of cancer in survivors of pediatric ESRD. *Clin J Am Soc Nephrol.* 2015;10:2198–2204.
9. Francis A, Johnson DW, Craig JC, et al. Incidence and predictors of cancer following kidney transplantation in childhood. *Am J Transplant.* 2017;17:2650–2658.
10. Serrano OK, Bangdiwala AS, Vock DM, et al. Post-transplant malignancy after pediatric kidney transplantation: retrospective analysis of incidence and risk factors in 884 patients receiving transplants between 1963 and 2015 at the University of Minnesota. *J Am Coll Surg.* 2017;225:181–193.
11. Motoyama O, Hasegawa A, Ohara T, et al. A prospective trial of steroid withdrawal after renal transplantation treated with cyclosporine and mizoribine in children: results obtained between 1990 and 2003. *Pediatr Transplant.* 2005;9:232–238.
12. Hasegawa A, Oshima S, Takahashi K, et al. Successful treatment of 115 pediatric renal transplant recipients with tacrolimus-based immunosuppressive therapy: a 7-year multicenter study in Japan. *Transplant Proc.* 2005;37:1769–1770.
13. Nagasawa T, Miura K, Kaneko N, et al. Long-term outcome of renal transplantation in childhood-onset anti-neutrophil cytoplasmic antibody-associated vasculitis. *Pediatr Transplant.* 2020;24:e13656.
14. Tanabe K, Takahashi K, Sonda K, et al. Long-term results of ABO-incompatible living kidney transplantation: a single-center experience. *Transplantation.* 1998;65:224–228.
15. Ohta T, Kawaguchi H, Hattori M, et al. ABO-incompatible pediatric kidney transplantation in a single-center trial. *Pediatr Nephrol.* 2000;14:1–5.
16. Hattori M, Mieno M, Shishido S, et al. Outcomes of pediatric ABO-incompatible living kidney transplantations from 2002 to 2015: an analysis of the Japanese Kidney Transplant Registry. *Transplantation*. 2018;102:1934–1942.
17. Ohta T, Kawaguchi H, Hattori M, et al. Effect of pre-and postoperative plasmapheresis on posttransplant recurrence of focal segmental glomerulosclerosis in children. *Transplantation.* 2001;71:628–633.
18. Chikamoto H, Hattori M, Kuroda N, et al. Pretransplantation combined therapy with plasmapheresis and rituximab in a second living-related kidney transplant pediatric recipient with a very high risk for focal segmental glomerulosclerosis recurrence. *Pediatr Transplant.* 2012;16:E286–E290.
19. Sato T, Fujieda M, Tanaka E, et al. Monitoring of Epstein-Barr virus load and antibody in pediatric renal transplant patients. *Pediatr Int.* 2008;50:454–458.
20. Ishihara M, Tanaka E, Sato T, et al. Epstein-Barr virus load for early detection of lymphoproliferative disorder in pediatric renal transplant recipients. *Clin Nephrol.* 2011;76:40–48.
21. Paya CV, Fung JJ, Nalesnik MA, et al. Epstein-Barr virus-induced posttransplant lymphoproliferative disorders. ASTS/ASTP EBV-PTLD Task Force and The Mayo Clinic Organized International Consensus Development Meeting. *Transplantation.* 1999;68:1517–1525.
22. Hu M, Zhang GY, Arbuckle S, et al. Prophylactic bilateral nephrectomies in two paediatric patients with missense mutations in the WT1 gene. *Nephrol Dial Transplant.* 2004;19:223–226.
23. Ezaki J, Hashimoto K, Asano T, et al. Gonadal tumor in Frasier syndrome: a review and classification. *Cancer Prev Res (Phila).* 2015;8:271–276.
24. Hori M, Matsuda T, Shibata A, et al; Japan Cancer Surveillance Research Group. Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Jpn J Clin Oncol.* 2015;45:884–891.
25. Hattori M, Mieno M, Aikawa A, et al. Demographic data and outcomes of pediatric kidney transplantations in Japan [article in Japanese]. *Jpn J Transplant*. 2016;51:452–839.
26. Mudigonda T, Levender MM, O'Neill JL, et al. Incidence, risk factors, and preventative management of skin cancers in organ transplant recipients: a review of single- and multicenter retrospective studies from 2006 to 2010. *Dermatol Surg.* 2013;39(Pt 1):345–364.
27. Arnold AW, Hofbauer GF. Human papillomavirus and squamous cell cancer of the skin—epidermodysplasia verruciformis-associated human papillomavirus revisited. *Curr Probl Dermatol.* 2012;43:49–56.
28. Kasiske BL, Snyder JJ, Gilbertson DT, et al. Cancer after kidney transplantation in the United States. *Am J Transplant.* 2004;4:905–913.
29. Vajdic CM, McDonald SP, McCredie MR, et al. Cancer incidence before and after kidney transplantation. *JAMA.* 2006;296:2823–2831.
30. Adami J, Gäbel H, Lindelöf B, et al. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. *Br J Cancer.* 2003;89:1221–1227.
31. Hoshida Y, Tsukuma H, Yasunaga Y, et al. Cancer risk after renal transplantation in Japan. *Int J Cancer.* 1997;71:517–520.
32. Cheung CY, Lam MF, Chu KH, et al. Malignancies after kidney transplantation: Hong Kong renal registry. *Am J Transplant.* 2012;12:3039–3046.
33. Li WH, Chen YJ, Tseng WC, et al. Malignancies after renal transplantation in Taiwan: a nationwide population-based study. *Nephrol Dial Transplant.* 2012;27:833–839.
34. Agbai ON, Buster K, Sanchez M, et al. Skin cancer and photoprotection in people of color: a review and recommendations for physicians and the public. *J Am Acad Dermatol.* 2014;70:748–762.
35. Steliarova-Foucher E, Colombet M, Ries LAG, et al; IICC-3 contributors. International incidence of childhood cancer, 2001-10: a population-based registry study. *Lancet Oncol.* 2017;18:719–731.
36. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68:394–424.
37. Apalla Z, Lallas A, Sotiriou E, et al. Epidemiological trends in skin cancer. *Dermatol Pract Concept.* 2017;7:1–6.
38. Mynarek M, Schober T, Behrends U, et al. Posttransplant lymphoproliferative disease after pediatric solid organ transplantation. *Clin Dev Immunol.* 2013;2013:814973.
39. Dharnidharka VR, Sullivan EK, Stablein DM, et al; North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Risk factors for posttransplant lymphoproliferative disorder (PTLD) in pediatric kidney transplantation: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *Transplantation.* 2001;71:1065–1068.
40. Fujieda M, Hattori M. Cancer-infection interface in children after transplantation: posttransplant lymphoproliferative disorder and Epstein-Barr virus infection. *Curr Opin Organ Transplant.* 2013;18:549–554.
41. Le J, Durand CM, Agha I, et al. Epstein-Barr virus and renal transplantation. *Transplant Rev (Orlando).* 2017;31:55–60.