Elevated Risk of Cancer After Solid Organ Transplant in Childhood: A Population-based Cohort Study

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Background. Cancer risk is elevated among adult transplant recipients, but there is limited data regarding long-term cancer risk and mortality in pediatric recipients. **Methods.** We conducted a population-based retrospective cohort study in Ontario, Canada. We included pediatric recipients of solid organ transplants at the Hospital for Sick Children, Toronto, from 1991 to 2014, and compared rates of new cancers and cancer-specific mortality to nontransplanted Ontario children born in the same year. We constructed standard and time-dependent Cox proportional hazards models accounting for competing risk of death. **Results.** A total of 951 recipients (kidney, n = 400; liver, n = 283; heart, n = 218; lung, n = 36; multiorgan/small bowel, n = 14) were compared with 5.3 million general population children. Mean (SD) age was 8.2 (6.4) years; 50% were male. Over a mean (SD) follow-up of 10.8 (7.1) years, cumulative incidence of cancer was 20% in recipients and 1.2% in the general population (incidence rate ratio, 32.9; 95% confidence interval [CI], 26.6–40.8). Risk was highest in the first year posttransplant (adjusted hazard ratio [aHR],176; 95% CI, 117–264), but remained elevated beyond 10 years (aHR, 10.8; 95% CI, 6.3–18.6). Lymphoproliferative disorders were predominant (77%); however, solid cancers (renal, sarcomas, genital, thyroid) were seen. Recipients of lung or multiorgan transplants were at highest risk. Cancer-specific mortality was also higher among recipients (HR, 93.1; 95% CI, 59.6–145.2). **Conclusions.** Childhood transplant recipients have a 30 times greater cancer incidence versus the general population. Further investigation is needed to guide screening strategies in this at-risk population.

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Chronic immunosuppression after solid organ transplantation increases the risk for subsequent cancer.[1,2] An increased risk of malignancy was observed as early as 4 years posttransplantation.[1] Much of the information regarding the incidence of posttransplant neoplasms is derived from multicenter registries of adult transplant recipients. Rates of posttransplant lymphoproliferative disorders (PTLD) and cancers of the skin, colon, lung, and kidney are elevated in adult recipients[3-7] with standardized incidence ratios (SIRs) relative to the general population ranging between 1.97 and 11.6.[6] Smaller population-based cohorts have estimated a twofold to fourfold increase in cancer risk.[8-14] There is limited published data regarding cancer incidence and subsequent survival in pediatric

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transplant recipients despite a potentially higher cancer incidence than that in adult recipients.[15]

Childhood solid organ transplant recipients may be at greater malignancy risk than adult counterparts for multiple reasons. Childhood recipients undergo immunosuppression at ages when their immune systems have not yet matured and often require retransplantation with additional induction immunosuppression and maintenance therapy. Perhaps most importantly, childhood organ transplant recipients may be naive to oncogenic viral infections, such as Epstein-Barr virus (EBV), at the time of transplantation, and consequently are at relatively higher risk of posttransplant lymphoproliferative disorders than adult recipients.[16,17]

The cumulative incidence of malignancy in adult solid organ transplant recipients increases over time, reaching 20% after 10 years and almost 30% after 20 years post-kidney transplantation.[5] This is of particular concern for childhood recipients with potentially several decades of life expectancy posttransplant. Although adult data cannot be directly extrapolated to children, these findings suggest that adolescent transplant recipients may develop cancers much earlier than the general population (ie, in their thirties and forties). Despite this concern, there are currently no targeted screening programs specific to this population, and limited data to inform the development of screening strategies. Most adult posttransplant programs use general population screening guidelines (with the addition of annual skin cancer screening), which may be suboptimal given the potential earlier ages at which cancers develop posttransplant.

Previous studies of cancer incidence in childhood transplant recipients have also lacked a contemporaneous general population comparator. Most studies have used expected, rather than observed cancer rates to calculate SIRs. This may not account for temporal trends and environmental factors that influence cancer risk. Recent studies also suggest rising incidence rates of specific cancers, including lymphomas and thyroid cancers, among children and adolescents.[18,19] To address these issues, we conducted a population-based cohort study to assess both cancer incidence and subsequent cancer-related mortality in childhood recipients of solid organ transplants compared with the general population.

MATERIALS AND METHODS

Study Subjects

The study included all recipients of solid organ (kidney, liver, heart, lung and multiorgan) transplants performed between July 1, 1991, and December 31, 2014, at the Hospital for Sick Children, Toronto, which has the largest and most comprehensive multiorgan pediatric transplant program in Canada and conducts over 89% of pediatric organ transplants in Ontario (Canada's most populous province).[20]

For comparison, we used linked population-level provincial administrative data housed at the Institute for Clinical Evaluative Sciences (ICES) to identify nontransplanted children from the general population. The Ontario Health Insurance Program (OHIP) Registered Persons Database, which contains demographic information as well as birth and death dates for all Ontario residents, was used to identify all Ontario children (without history of solid organ transplantation) that were born in the same birth years as the individuals in the transplanted group. OHIP is the single payer for universal access to hospital care and physician services to Ontario's 13 million residents. In order to ensure adequate ascertainment of outcomes, we included only individuals with evidence of OHIP eligibility throughout the follow-up period and no gaps in OHIP coverage eligibility of greater than 1 year. The Canadian Organ Replacement Register (a national registry containing data on 98% of organ transplants in Canada[21]) was used to exclude those with a previous history of solid organ transplantation from other centers and also allograft failure (ie, chronic dialysis or retransplantation) in kidney transplant recipients.

Children with preexisting malignancy or previous bone marrow transplant, and those residing in non-Ontario provinces were excluded from both groups due to the inability to discern incident cancer outcomes (vs preexisting malignancies) and the inability to ascertain cancer outcomes from other provincial registries.

This study was approved by the institutional review board at the Hospital for Sick Children.

Outcomes and Outcome Assessment

Cancer diagnoses were ascertained using the Ontario Cancer Registry (OCR), which contains information on all incident cancers in Ontario, excluding nonmelanoma skin cancers, and were estimated to be more than 95% complete.[22] Ontario Cancer Registry captures incident cancers, but does not register recurrences of previously diagnosed malignancies. Cancer diagnoses were encoded according to *International Classification of Diseases Oncology 3rd revision* (ICD-O-3) codes. Where applicable, both ICD-O-3 topographical site and morphologic codes were used (**Table S1, S2 and S3, SDC**, http://links.lww.com/TP/B609). Cancer diagnoses in the transplant group were further adjudicated to confirm cancer classification by 2 pediatric oncologists (S.G. and P.N.), who reviewed cancer topographical and morphologic diagnostic codes and dates of diagnoses to ensure primary cancer types and sites were accurately ascribed.

The primary outcome was the incidence of any cancer after the date of transplantation, which served as the index date. Individuals in the nontransplanted comparator group were randomly assigned an index date based on the distribution of transplant dates among transplant recipients with the same birth year and sex. Subjects were not censored after the first cancer diagnosis; thus, subsequent new cancer diagnoses were also captured.

Secondary outcomes included the incidence of solid cancers and PTLD (defined in our study as lymphomas/lymphoid malignancies). Additional secondary outcomes were all-cause mortality using Registered Persons Database and cancer-related mortality using OCR and the Office of the Registrar General of Ontario Death Register. Agreement on malignancy-related cause of death between the OCR and a prospective cohort with intensive clinical follow-up was high, with estimated sensitivity of 95% and specificity of 88%.[23] This method was previously used to establish cancer-specific mortality among transplant recipients.[24]

Statistical Analyses

Cancer incidence was reported as events per 1000 patient-years of follow-up, as well as incidence rate ratios (IRR) and 95% confidence intervals (CI), with the nontransplant group as the referent. We used standard Cox models and time-dependent Cox proportional hazards models to estimate hazard ratios (HR) and 95% CI for incident cancers and mortality. The standard Cox model provided an average HR across the entire follow-up period, whereas the time-dependent model assessed HRs within specific time strata after the index date. Analyses of cancer incidence and cancer-specific mortality outcomes were performed accounting for the competing risks of death by the Fine and Gray method.[25] For the time-dependent Fine and Gray models, to avoid computational processing issues related to model complexity, a subset of the unexposed cohort (a random sample of 1 000 000 individuals) was used. Parameter estimates were then confirmed using the full cohort for the cancer incidence (primary outcome) models. We used multivariable models with adjustment for age at transplant, sex (male as referent), and year of transplant. We performed subgroup analyses by type of solid organ transplanted. We verified the proportional hazards assumption statistically with Schoenfeld residuals, ranked failure times and also graphically by log-log survival curves.

We performed additional analyses by era of transplant, from 1991 to 2000 and 2001 to 2014. This division in era approximately corresponds with widespread use of newer calcineurin inhibitors, although individual immunosuppressive protocols varied across organ types and at the discretion of treating physicians.

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). A 2-sided *P* value less than 0.05 was considered statistically significant.

RESULTS

We identified 951 childhood solid organ transplant recipients without evidence of prior malignancy between July 1, 1991, and December 31, 2014, 400 kidney, 283 liver, 218 heart, 36 lung, and 14 other (multiorgan or small bowel) transplants. The nontransplant group consisted of 5 276 621 individuals from the general population with the same birth year. Those excluded from the cohort on the basis of each exclusion criterion are shown in Figure 1. Demographic data, organ type, and transplant characteristics are shown in Table 1. Additional data on general cause of organ failure, induction therapy, and immunosuppression for the transplanted group are shown in **Table S1, SDC** (http://links.lww.com/TP/B609). The median age (interquartile range [IQR]) at index in both groups was 8 (1–14), with 54% and 50% males in the transplant and nontransplant groups, respectively. Approximately two thirds of transplants occurred in the 2001 to 2014 era and the majority of transplants were from deceased donors (72%).

Cancer Incidence

The mean (standard deviation [SD]) follow-up was 10.8 (7.1) years in the nontransplant group and 8.4 (6.5) years in the transplanted group, representing 56 961 373 total person-years of follow-up. There were 18353 cancer diagnoses in the nontransplant group and 84 cancers in the transplant group. The mean time to incident cancer diagnosis was 5.0 years (SD, 5.4) in transplanted and 11.1 years (SD, 6.4) in nontransplanted children. The mean (SD) age at cancer diagnosis was 12.8 years (8.1) in the transplant group and 23.2 (9.5) years in the nontransplant group.

The event rate for all cancers (95% CI) was 10.6 (8.5–13.1) and 0.3 (0.3–0.3) per 1000 patient-years in the transplant and nontransplant groups, respectively. The IRRs of all cancers (95% CI) was 32.9 (26.6–40.8). Unadjusted and adjusted hazard ratios over the entire 24 years of follow-up for all cancers (95% CI) were 37.3 (29.8–46.7) and 41.5 (33.1–52.0), respectively. The IRR for solid cancers (95% CI) was 10.6 (7.0–16.2), with adjusted HR of 14.0 (95% CI, 9.1–21.3). The IRR for lymphoproliferative disorders was considerably higher at an HR of 128.4 (95% CI, 99.9–165.1) with adjusted HR of 137.6 (95% CI, 106.2–178.1). Cancer incidences, overall event rates (per 1000-patient-years), and hazard ratios are summarized in Table 2. Incidence curves for (all) cancers and all-cause mortality are shown in Figure 2. Posttransplant lymphoproliferative disorders and solid cancer incidence curves for the transplanted group are shown in Figure 3.

We tested the proportional hazards assumption for each of our models and found that the hazards for all cancers, lymphoproliferative disorders, and all-cause death were nonproportional over the full follow-up. Therefore, we calculated HRs for smaller clinically relevant time strata (0–1, 1–5, 5–10, and > 10 years) during which the hazards remained proportional. The HRs in each stratum are

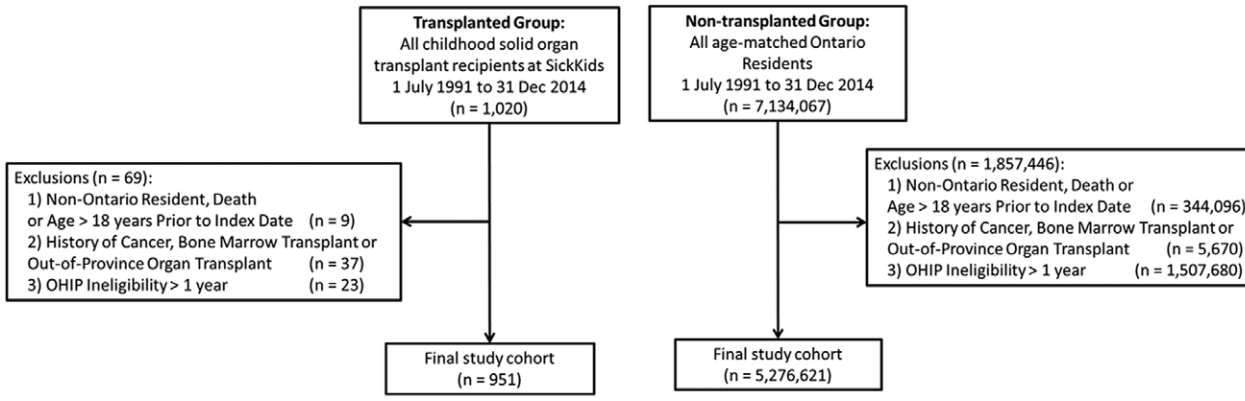

FIGURE 1. Flow diagram of cohort assembly of transplanted and nontransplanted individuals from 1991 to 2014.

TABLE 1.

Baseline demographic, organ type and donor status of transplanted and nontransplanted individuals in Ontario from 1991 to 2014

Characteristics	Transplanted		Nontransplanted	
Patients	n = 951		n = 5 276 621	
Age, y				
mean (SD)	7.8	6.2	8.2	6.4
Median (IQR)	8	(1–14)	8	(1–14)
Males	514	54.0%	2 630 154	49.8%
Era				
1991–2000	305	32.1%	1 807 385	34.3%
2001–2014	646	67.9%	3 469 236	65.7%
Organ type				
Heart	218	22.9%		
Kidney	400	42.1%		
Liver	283	29.8%		
Lung	36	3.80%		
Other (bowel/multiorgan)	14	1.50%		
Type of donor				
Deceased	685	72.0%		
Living	265	27.9%		

summarized in Table 3. The relative hazard for cancer was highest in the first-year posttransplant, with an adjusted HR of 175.7 (95% CI, 116.9–264.0). Although the relative hazard diminished over follow-up, it remained significantly elevated throughout the remaining time strata. Separate HRs for solid cancers and lymphoproliferative disorders in each time strata are shown in **Table S5, SDC** (http://links.lww.com/TP/B609).

We also performed analyses by era of transplant (1991 to 2000 versus 2001 to 2014) and found that the risk of cancer in transplant recipients was higher in the latter era, with aHR of 21.3 (95% CI, 15.5–29.2) versus 48.6 (95% CI, 35.6–66.3) (*P* value for interaction is 0.01).

Cancer Types

The most common cancer type seen in the transplant group was PTLD (with 65 diagnoses, representing 77% [68–86%] of cancers). Other hematologic cancers were the next most common diagnosis within the transplant group (6 diagnoses or 7% [2–13%]). Other cancers in the transplant group, in descending order of frequency, included renal, sarcoma, female genital, head and neck, hepatobiliary and thyroid cancers. There were 6 individuals in the transplanted group who developed 2 cancer diagnoses (and none with more than 2 cancers). In the nontransplant group, thyroid cancers were most common with 2877 diagnoses (or 16% [15–16%] of cancers), followed by lymphomas with 2795 diagnoses (15% [15–16%) of cancers) (Table 4).

Cancer Risk by Organ Transplant Type

We grouped lung, small bowel, and multiorgan transplant recipients when assessing cancer risk by type of organ transplanted (Table 5). This group had the highest proportion of patients with cancer diagnoses [20%, 95% CI (9, 31%)], followed by heart [14%, (9, 18%)], liver [7% (4, 10%)], and kidney [6% (4, 9%)]. In adjusted Cox regression the lung, small bowel and multiorgan transplant and heart transplant group had increased risk of cancer relative to kidney recipients (aHR, 3.08; 95% CI, 1.83,-5.19) and 6.27; 95% CI, 2.93–13.4, respectively). Mean age at cancer was lowest in liver recipients 9.2 (SD, 7.8) and highest among kidney recipients 18.3 (SD, 7.9). In kidney transplant recipients, we were able to ascertain allograft failure (including chronic dialysis or retransplantation), which occurred in 128 recipients. Of the 25 cancer diagnoses in kidney recipients, the majority (19 [76%]) occurred before allograft failure.

Cancer-specific Mortality

There were 19 cancer-attributed deaths in the transplant group (23% of those with cancer diagnoses) and 1784 in the nontransplant group (10% of those with cancer diagnoses). Of the 19 cancer-related deaths in the transplanted group, 13 (68%) occurred in patients with PTLD, with the remaining deaths associated with solid cancer diagnoses.

The hazard of cancer-specific mortality was higher in transplanted individuals with an adjusted HR of 93.1 (95% CI, 59.6–145.2). The risk of all-cause mortality and noncancer mortality were similarly elevated, with adjusted HRs of 78.2 (95% CI, 66.3–92.4) and 77.7 (95% CI, 65.1–92.7), respectively. Time-stratified HRs for all-cause and cancer-specific mortality are shown in Table 3 and cumulative incidence function values in Table 4. The time-stratified results for cancer-specific mortality should be interpreted with caution due to the small number of events within the exposed group.

DISCUSSION

The risk of cancer among childhood solid organ recipients is approximately 30 times higher than that observed in the general population over 24 years. This level of

TABLE 2.

Summary of cancer incidence estimates in transplanted and nontransplanted individuals from 1991 to 2014

	Transplanted	Nontransplanted
Person-years of follow-up	7956	56 953 417
Mean follow-up (SD)	8.4 (6.5)	10.8 (7.1)
Mean age at cancer (SD)	12.8 (8.1)	23.2 (9.5)
All cancers		
Mean years to cancer (SD)	5.0 (5.4)	11.1 (6.4)
Event rate/1000 patient-years (95% CI)	10.6 (8.5–13.1)	0.3 (0.3–0.3)
IRR (95% CI)	32.9 (26.6–40.8)	Reference
Solid cancers		
Mean years to solid cancer (SD)	5.4 (5.7)	11.5 (6.4)
Event rate/1000 patient-years (95% CI)	2.8 (1.8–4.2)	0.3 (0.3–0.3)
IRR (95% CI)	10.6 (7.0–16.2)	Reference
Lymphoma/PTLD		
Mean years to lymphoma/PTLD (SD)	4.9 (5.4)	9.3 (6.0)
Event rate/1000 patient-years (95% CI)	7.8 (6.1–10.0)	0.1 (0.1–0.1)
IRR (95% CI)	128.4 (99.9–165.1)	Reference

*Adjusted for age at transplant, sex, and year of transplantation.

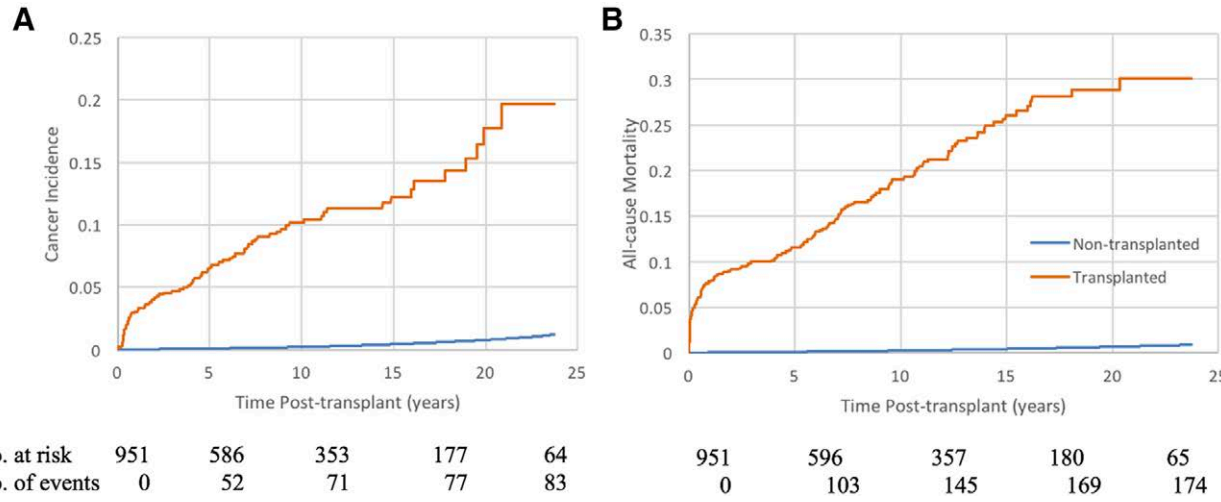

FIGURE 2. Incidence curves for (A) all cancers diagnoses; (B) all-cause mortality among pediatric transplant recipients and the age-matched general population.

relative risk is considerably higher than that observed in adult transplant recipients.[8-14] Although the majority of cancers observed were lymphoproliferative disorders, the incidence of solid cancers was also elevated. The rate of malignancy was highest in the early period posttransplant and in those who received lung or multiorgan and heart transplants. Cancer-specific mortality was also considerably higher among transplanted individuals.

Previously combined adult and pediatric cohorts have suggested that younger transplant recipients are at increased cancer risk. A large multiple organ registry study reported that the relative risk of non-Hodgkin's lymphoma, liver and renal cancers were highest in the youngest age category (<35 years of age), with SIR point estimates of 46, 28, and 17, respectively.[6] Others have shown that kidney transplant recipients younger than 35 years had the highest standardized rate ratio for cancer compared to older recipients, with standardized rate ratios ranging from 15 to 30.[4] Our results are congruent with these studies, and suggest an inverse relationship between age at transplant, especially in the very young, and the subsequent relative hazard of cancer.

On average, approximately 1 in 5 childhood transplant recipients in our cohort will develop cancer by the age of 30 years. Moreover, in our data, transplants recipients who were 10 years from transplantation (ie, a median 18 years of age), had an absolute cancer incidence rate of 2.4 cases per 1000 patient-years. This cancer rate is comparable to that seen in Ontario general population residents aged 60 to 69 years (who have a reported age-specific cancer incidence of approximately 2.7 cases per 1000 individuals).[26]

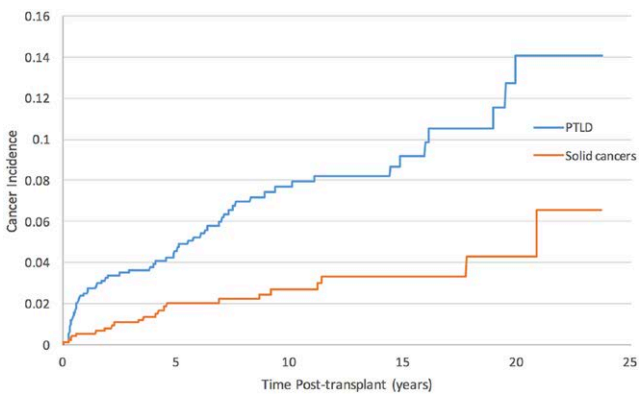

FIGURE 3. Incidence curves of solid cancers and posttransplant lymphoproliferative disorders (PTLD) among childhood transplant recipients.

There are limited data specific to cancer risk in childhood transplant recipients. A recent study of 17958 US pediatric solid organ transplant recipients reported an SIR for non-Hodgkin lymphoma of 212, which represented 71% of cancers in this population.[27] A population-based study of pediatric organ recipients in Sweden with 537 individuals and 24 cancer events demonstrated lower overall cancer risk than in our study with a SIR for all cancers of 12.5. However, consistent with our data, the risk of non-Hodgkin lymphoma was very elevated with a SIR of 127.[28] Similar findings have been observed in single-organ transplant cohorts, with reported IRR or SIR ranging from 18 to 22 for all cancers, and over 120 for non-Hodgkin lymphoma.[29,30] Francis et al[31] reported a cumulative incidence of malignancy of 27% at 25 years posttransplant for childhood kidney recipients (with PTLD again being the most common cancer observed).

Although lymphoproliferative disorders are the predominant cancer risk in transplant recipients, our data suggest a significant risk of solid cancers among transplanted children. Numbers of individual cancer types were low; however, the presence of female genital, renal and thyroid cancers suggest that further investigation is needed to assess the clinical utility of targeted cancer screening strategies in this at-risk population, especially as children age. Similar cancer types, including hematologic, female genital, and renal cancers were also noted to be more common in other pediatric cohorts.[28]

With respect to risk conferred by organ type, we observed that lung (grouped with small bowel and multiorgan) and heart recipients had the highest risks of subsequent malignancy. This is in keeping with results in adult recipients[6,10,32] and, in the case of lung and multiorgan recipients, could be related to the relative degree of immunosuppression used. With respect to heart recipients, these transplants often occur at younger ages, and the proportion of EBV naive children could account for

TABLE 3.

Time-stratified hazard ratios for cancer incidence, cancer-specific mortality, and all-cause mortality

	0–1 y	1–5 y	5–10 y	>10 y
Cancer incidence				
No. transplant recipients at risk (n)	951	814	586	353
Absolute event rate (per 1000 PY)				
Transplanted (95% CI)	31.2 (21.5–45.2)	6.9 (4.7–10.3)	3.6 (2.3–5.7)	2.4 (1.4–4.1)
Nontransplanted (95% CI)	0.2 (0.2–0.2)	0.1 (0.1–0.1)	0.1 (0.1–0.1)	0.2 (0.2–0.2)
Unadjusted HR	168.3 (112.0–252.6)	42.4 (28.5–63.2)	29.6 (18.8–46.7)	9.3 (5.4–15.9)
aHR[a]	175.7 (116.9–264.0)	45.4 (30.3–67.7)	32.6 (20.7–51.6)	10.8 (6.3–18.6)
Cancer-specific mortality				
Absolute event rate (per 1000 PY)				
Transplanted (95% CI)	6.5 (2.9–14.3)	1.1 (0.4–2.9)	1.3 (0.6–2.8)	0.5 (0.2–1.7)
Nontransplanted (95% CI)	0.03 (0.02–0.03)	0.02 (0.02–0.02)	0.01 (0.01–0.01)	0.02 (0.02–0.02)
Unadjusted HR	451.6 (116.7–1747.7)	45.0 (14.2–142.8)	94.9 (46.1–195.3)	45.2 (20.0–101.9)
aHR*	479.6 (124.2–1851.6)	48.9 (15.4–155.6)	105.5 (51.1–217.5)	52.9 (23.4–119.2)
All-cause mortality				
Absolute event rate (per 1000 PY)				
Transplanted (95% CI)	87.3 (70.9–107.4)	8.8 (6.3–12.4)	6.8 (4.9–9.5)	4.7 (3.2–6.9)
Nontransplanted (95% CI)	0.3 (0.3–0.3)	0.2 (0.2–0.2)	0.1 (0.1–0.1)	0.2 (0.2–0.2)
Unadjusted HR	342.8 (263.7–7445.6)	45.7 (31.6–66.3)	65.9 (48.3–89.9)	36.4 (25.2–52.6)
aHR[a]	343.6 (263.3–448.4)	46.4 (32.0–67.4)	67.8 (49.6–92.7)	37.6 (25.9–54.7)

[a] Adjusted for age at transplant, sex, and year of transplantation.

the excess cancer risk observed in this group. Similarly, the increase in cancer incidence seen in the more recent era (2001 to 2014) may reflect changes in immunosuppression regimens and improved cancer detection at earlier stages. Conversely, this trend may reflect better graft and patient survival, which allows greater time for both cancer development and diagnosis.[32]

Our findings suggest that the relative cancer risk is highest in the first 5 years, and particularly in the first year after transplant. Induction immunosuppression and higher intensity of maintenance immunosuppression may be partly attributable, particularly with antithymocyte globulin, which is implicated in PTLD risk.[28,33] Perhaps even more significant in children is primary infection with oncogenic viruses, such as EBV after transplantation, which may considerably increase the subsequent risk of lymphoproliferative disorders.[34,35] Data suggest that 60% to 80% of EBV naïve transplant recipients will convert to EBV positivity within 3 months of transplant,[36] potentially leading to early occurrence of PTLD in children. Our study highlights the importance of monitoring for malignancy in the early period posttransplant.

The relative hazard of cancer diminishes as time from transplant increases. This may be partly due to the early posttransplant risks of induction immunosuppression and oncogenic infections; however, this pattern may also be explained by the fact that the risk of cancer is very low in the young, and ostensibly in the healthy, general population. As the general population ages, their risk of morbidities (including cancer) increases, and therefore the relative hazard of cancer (and other comorbid conditions) are expected to decrease over time.

Cancer-specific mortality was also markedly elevated in those transplanted versus the general population. Higher rates of cancer-mortality were observed in both adults and children posttransplant.[24,37,38] Comparable risk estimates were reported amongst pediatric subgroups of recipients, including cancer-specific standardized mortality ratios (SMR) as high as 85 times the general population.[24] Also, much of the cancer-related mortality in our cohort was

TABLE 4.

Cumulative incidence function values for cancer, cancer-specific mortality and all-cause mortality

Cumulative incidence (%, 95% CI)	1	5	10 (Years posttransplant)	15	20
All cancers					
Transplanted	2.88 (1.94–4.09)	6.01 (4.55–7.74)	9.19 (7.24–11.42)	10.86 (8.55–13.47)	15.07 (11.21–19.46)
Nontransplanted	0.01 (0.01–0.02)	0.09 (0.08–0.10)	0.21 (0.20–0.23)	0.42 (0.40–0.45)	0.75 (0.71–0.79)
Cancer-specific mortality					
Transplanted	0.65 (0.27–1.35)	1.17 (0.6–2.09)	2.39 (1.43–3.76)	3.28 (1.98–5.09)	3.28 (1.98–5.04)
Nontransplanted	0.00 (0.00–0.00)	0.01 (0.01–0.02)	0.03 (0.02–0.03)	0.05 (0.04–0.05)	0.07 (0.07–0.08)
All-cause mortality					
Transplanted	7.87 (6.15–9.59)	11.58 (9.46–13.70)	19.05 (16.13–21.97)	26.10 (22.28–29.92)	28.90 (24.47–33.33)
Nontransplanted	0.02 (0.02–0.03)	0.11 (0.11–0.12)	0.25 (0.24–0.25)	0.44 (0.43–0.44)	0.68 (0.66–0.69)

TABLE 5.

Cancer risk by transplanted organ type

Transplanted organ	Patients, n (%)	Cancers, n (%)	aHR (95% CI)
Kidney	400 (42)	25 (6)	Referent
Liver	283 (30)	19 (7)	1.37 (0.75–2.47)
Heart	218 (23)	30 (14)	3.08 (1.83–5.19)
Other (lung, small bowel, multiorgan)	50 (5)	10 (20)	6.27 (2.93–13.4)

associated with PTLD diagnoses (68%). This suggests that as with adult solid organ recipients,[39] PTLD is associated with considerable mortality burden in the pediatric transplant population.

The higher risk of cancer-specific mortality likely reflects not only the increased incidence of cancer in the transplant recipient population but also potential differences in treatment options and overall comorbidity burden.[37] Certain cancer therapies may pose a risk for organ toxicity, which is of greater concern in transplant recipients, who have comorbid conditions such as chronic kidney disease, cardiovascular disease, and diabetes. This could result in suboptimal cancer treatment and increased mortality. The increased cancer-specific mortality observed lends further rationale for timely screening and diagnosis of cancer in this population.

At present, organ-specific clinical practice guidelines are able to provide limited recommendations regarding screening strategies for noncutaneous malignancies posttransplantation. Among kidney transplant recipients, the Kidney Disease: Improving Global Outcomes work group provides an ungraded recommendation for screening for breast, cervical, colon and prostate cancers as per local general population guidelines.[40] Similarly, guidelines for heart transplant recipients recommend following general population screening guidelines for these malignancies (except cervical cancer).[41] The American Society of Transplantation liver transplant guidelines recommend annual screening for colon cancer in patients with primary sclerosing cholangitis and hepatocellular carcinomas in those with cirrhotic allografts, but do not make recommendations for other nonskin cancers.[42] With significant mortality after cancer diagnosis in the transplant population, it may be prudent to initiate cancer screening earlier than currently recommended. Initiation of cancer screening at ages recommended for the general population (ages >50 years for colon and breast cancer screening[43]) may be too late for childhood recipients and that additional data are needed to evaluate whether age-, transplant organ-, and cancer-specific screening should be considered in this population. The Kidney Disease: Improving Global Outcomes and American Society of Transplant guidelines recommend monitoring for EBV seroconversion,[44] and our data support the need for close surveillance.

The strengths of our analysis include a population-level data set, with validated outcome ascertainment from a province-wide cancer registry. We were able to use time-to-event analysis to assess cancer risk across childhood recipients of various solid organ transplant types and generate cumulative incidence curves. Our analysis allowed for longitudinal assessment of malignancy risk in different eras and at varying time strata posttransplant. Also, in contrast to previous studies, our analysis made use of a contemporaneous general population cohort in order to provide observed rather than expected estimates of cancer incidence. Despite these strengths, our study has limitations. Our data do not systematically capture comorbidities, although we expect pediatric recipients have fewer comorbid illnesses than adults. We were also only able to adjust for (fixed) baseline characteristics, and as such, could not account for potential changes in the transplanted and nontransplanted groups over time. As with other investigations,[6,28,32] we were unable to assess associations between cancer risk and specific immunosuppressive regimens and oncogenic infection status. Moreover, OCR does not capture nonmelanoma skin cancers, thus, we underestimate the total incidence of malignant neoplasms in this population. Also, we limited our analysis to children without gaps in OHIP eligibility, and as such, it is possible that we excluded some infrequent healthcare system users. This may have biased our estimates toward an underestimation of malignancy risk. Lastly, the risk estimates observed in our study are imprecise and should be interpreted with caution due to the small absolute number of cancers and cancer-related deaths seen during follow-up. As such, the high relative risk estimates we observed should be viewed in the context of a small absolute number of cancer events. The lack of a nationwide cancer registry precluded a larger sample population for assessment.

Childhood solid organ transplant recipients have a 30 times higher increased risk of cancer compared with the general pediatric population. Monitoring recipients for signs of malignancy (especially lymphoma), particularly in the early period posttransplantation, is warranted. Further investigation is needed to assess specific cancer risk factors to develop cancer-specific and transplant organ-specific screening strategies.

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SUPPORTING INFORMATION (DESCRIPTION)

Additional Supporting Information may be found online in the supporting information tab for this article. Support information for this study includes: **Table S4, SDC,** (http://links.lww.com/TP/B609) (Demographic, cause of organ failure and initial immunosuppression data in transplant recipients 1991 to 2014), ICD-O-3 diagnostic codes for cancer [grouped according to cancer type (**Table S1, SDC,** http://links.lww.com/TP/B609)], topographical (**Table S2, SDC,** http://links.lww.com/TP/B609) and morphological (**Table S3**) cancer code descriptions, and the RECORD statement checklist (**Materials and Methods, SDC,** http://links.lww.com/TP/B609).

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