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Cancer risk following post-transplant lymphoproliferative disorders in solid organ transplant recipients

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Keywords

Solid organ transplant recipients; post-transplant lymphoproliferative disorders; second primary cancers; non-Hodgkin lymphoma; lymphoid malignancies

Post-transplant lymphoproliferative disorders (PTLDs) are associated with immunosuppressive therapy administered to prevent graft rejection, leading to uncontrolled replication of Epstein–Barr virus (EBV) (Dierickx and Habermann 2018). Solid organ transplant (SOT) recipients also have increased risks of other malignancies, particularly those with viral aetiologies (Engels, *et al* 2011). In the general population, lymphoma survivors have increased risk of subsequent cancers due to lymphoma treatment, underlying immune dysfunction or shared risk factors (Baras, *et al* 2017, Morton, *et al* 2010). We conducted the first assessment of cancer risk after PTLDs among SOT recipients and compared patterns to previous literature describing cancer risks after lymphoma in the general population.

The Transplant Cancer Match Study links the US Scientific Registry of Transplant Recipients (SRTR) with 17 cancer registries (1987–2014), covering ~50% of the US SOT population (Table I) (Engels, *et al* 2011). We excluded recipients with a cancer diagnosis

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Author contributions

PM and LMM developed the concept; PM performed statistical analyses; LMM supervised data analyses; EAE and LMM supervised the project; PM, EAE, CFL, LMM provided critical intellectual content and drafted the manuscript. All authors reviewed and approved the final manuscript.

Disclosure of Conflicts of Interest

The authors of this manuscript have no conflicts of interest to disclose.

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before transplant (N=19,438), a transplant before the start of cancer registry coverage (N=7,542), human immunodeficiency virus infection (N=469), or (for liver transplants) a diagnosis of liver cancer ≤6 months after transplant (N=1,280, probably representing prevalent liver cancers).

PTLD was ascertained from: 1) linked cancer registries for lymphoid malignancies, identified using International Classification of Diseases for Oncology, edition 3 (ICD-O-3) morphology codes (Turner, *et al* 2010), and 2) SRTR post-transplant follow-up files [updated at 6 and 12 months following transplantation and annually thereafter; includes both monomorphic as well as polymorphic PTLDs not reportable to cancer registries]. We defined PTLD according to the World Health Organization (Swerdlow, *et al* 2016) plus lymphocytic leukaemias, because they are lymphoid neoplasms. We analysed PTLDs overall, as well as lymphoid malignancies and polymorphic PTLDs separately. We ascertained first malignant non-PTLD cancers from the linked cancer registries according to ICD-O-3 topography and morphology codes (Howlader, *et al* 2017). We analysed cancer risk overall and for specific types with ≥100 cases.

Included SOT recipients (N=235,775) were predominantly male (60.9%), non-Hispanic white (61.7%), had a median age of 48 years and more frequently received a kidney (59.8%) (Table I). During follow-up, 3,591 recipients were diagnosed with PTLD of any type (Table S1). Using Cox regression, we estimated PTLD risk with age as the time scale (Table I). PTLD risk was elevated among males, non-Hispanic whites, recipients of induction immunosuppression with alemtuzumab or muromonab-CD3, EBV seronegative recipients at the time of transplant and recipients of organs other than kidney.

We evaluated risk of non-PTLD cancer following PTLD using Cox regression (see Figure 1, footnote). Compared with recipients without PTLD, those with PTLD were more likely to be diagnosed with any subsequent non-PTLD cancer [adjusted hazard ratio (aHR)=1.6, 95% confidence interval (CI)=1.4–1.9; Figure 1]. Specifically, risk was elevated for cancers of the oesophagus, colon, liver, kidney, central nervous system and thyroid; non-lymphocytic leukaemia (including myelodysplasia and myeloproliferative neoplasms) and miscellaneous cancers. Overall cancer risk was elevated after lymphoid malignancies (N=2,917, aHR=1.5, 95%CI=1.3–1.8) and polymorphic PTLD (N=448, aHR=2.9, 95%CI=1.8–4.7) (Table S2).

For cancers where ≥10 PTLD cases were reported prior to diagnosis, we conducted additional exploratory analyses. Overall cancer risk following PTLD was similar irrespective of the organs transplanted, except for melanoma and kidney cancer, which were increased following PTLD only among kidney recipients (Table S3). In analyses by time since PTLD, risk was increased ≤6 months after PTLD for cancers overall (aHR=4.0, 95%CI=3.0–5.2) and for most evaluated cancers (Table S4). In contrast, cancer risks remained elevated >6 months after PTLD for kidney (aHR=2.0; 95%CI=1.1–3.5) and thyroid (aHR=3.9; 95%CI=1.7–8.8) cancers. In analyses by non-PTLD cancer stage at diagnosis, risks were more pronounced for localized/stage I cancers than regional/distant/stage II-IV cancers for kidney (aHR 2.3 vs. 0.7), thyroid (aHR 6.2 vs. 4.7) and colon cancers (aHR 3.6 vs. 1.7) (Table S5). Notably, most of the localized/stage I kidney and thyroid cancers were diagnosed >6 months after PTLD (Figure S1).

In this first comprehensive assessment of cancer risk following PTLD among SOT recipients, we observed increased risk of non-PTLD cancers overall, and also for specific types. Risks were primarily increased ≤6 months after PTLD diagnosis, suggesting that diagnostic and staging investigations following PTLD (such as positron-emission/computed tomography scans) may lead to identification of some of these cancers.

Notably, exceptions to this pattern were observed for kidney and thyroid cancer, for which risks persisted >6 months after PTLD diagnosis, which is consistent with the risks observed among non-Hodgkin lymphoma survivors in the general population (Baras, *et al* 2017). Due to the small number of PTLD cases, our results need to be replicated. Nonetheless, our results combined with general population data support a potential role for shared risk factors or lymphoid malignancy treatment in the aetiology of kidney and thyroid cancer. However, the lack of association between PTLD and lung cancer or melanoma except in some patient subgroups contrasts with results for lymphoma survivors in the general population (Baras, *et al* 2017, Engels, *et al* 2011, Morton, *et al* 2010).

SOT recipients have increased risk of virus-related cancers due to immunosuppressive medications, such as human papillomavirus-related anogenital cancers and hepatitis virus-related liver cancer (Engels, *et al* 2011). Except for liver cancer, risk of other virus-related cancers was not elevated following PTLD. Immunosuppression is an important risk factor for PTLD. However, reduction of immunosuppression is an essential part of PTLD treatment, and the subsequent partial restoration of immunity may explain the absence of increased risk of virus-related malignancies following PTLD.

Our study has some limitations. Because early lesions and polymorphic PTLDs are not captured by the cancer registries and the SRTR may miss some PTLD diagnoses, we may have under-ascertained PTLDs. We may have missed some cancers due to migration of transplant recipients from outside the cancer registry catchment area, or due to matching errors. Finally, PTLD generally is managed by reduced immunosuppression and intense chemotherapy, though some patients may be cured by reduced immunosuppression and rituximab alone (Evens, *et al* 2010). We could not analyse the effect of PTLD treatment on the risk of subsequent cancers due to lack of data on treatment.

PTLD occurrence is a serious clinical event associated with increased risk of mortality and graft failure (Dierickx and Habermann 2018). Our results highlight the need for awareness among clinicians regarding the increased likelihood of additional cancer diagnoses among individuals who develop PTLD. Some associations may be attributed to increased surveillance, but evidence of increased risk at longer latency intervals for kidney and thyroid cancer warrants further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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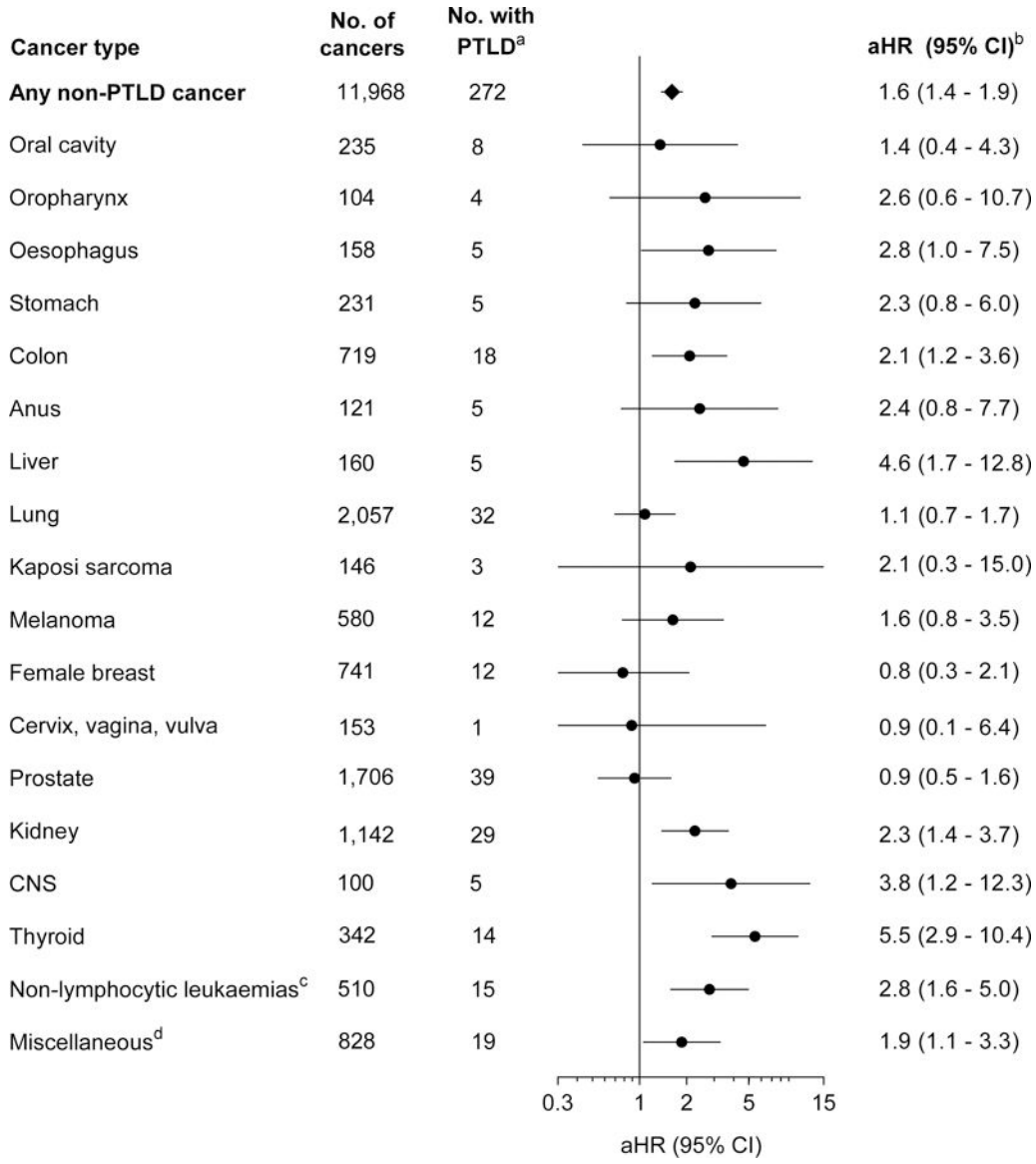

Figure 1: Cancer risk following PTLD among solid organ transplant recipients:

Cancer risks following PTLD are presented for specific cancer type as an adjusted hazard ratio and corresponding 95% confidence interval (horizontal axis, logarithmic scale).

Abbreviations: aHR, adjusted hazard ratio; CI, confidence intervals; CNS, central nervous system; PTLD, post-transplant lymphoproliferative disorder; SRTR, US Scientific Registry of Transplant Recipients

[a] Refers to the first occurrence of any type of PTLD in the SRTR or linked cancer registry

[b] Hazard ratios were obtained from Cox regression models with age as the time scale, PTLD diagnosis as a time-dependent variable, and adjusted for the following variables decided *a priori*: sex, race/ethnicity, year of transplant, transplanted organ, and time since transplantation (as a time-dependent variable). Follow-up began on the date of first transplantation and ended at the earliest of non-PTLD cancer diagnosis, graft failure, re-

transplantation, loss to follow-up, end of cancer registry coverage or death. Estimates did not change after additional adjustment for induction therapy or number of HLA mismatches.

[c] Non-lymphocytic leukaemias include myelodysplasias and myeloproliferative neoplasms.

[d] Miscellaneous includes cancers of other gastrointestinal tract sites (n=96), other respiratory tract organs (n=68), male breast (n=31), other female genitalia (n=82), other male genitalia (n=97), eye (n=30), other endocrine glands (n=15), leukaemia not otherwise specified (n=24) and unknown/uncertain primary cancers (n=385).

Table I:

Characteristics of solid organ transplant recipients[a] and risk factors for PTLD

Characteristics	Solid organ transplant recipients; n (%)	Cases of PTLD[b]; n (%)	aHR (95% CI)[c]
Total	235,775	3,591	
Age at transplant, years			
0 – 19	20,312 (8.6)	791 (22.0)	*c*
20 – 34	33,760 (14.3)	414 (11.5)	
35 – 49	70,962 (30.1)	765 (21.3)	
50 – 64	88,277 (37.4)	1,281 (35.7)	
65 +	22,464 (9.5)	340 (9.5)	
Sex			
Males	143,679 (60.9)	2,329 (64.9)	Reference
Females	92,096 (39.1)	1,262 (35.1)	0.8 (0.8 – 0.9)
Race/ethnicity			
Non-Hispanic white	145,479 (61.7)	2,657 (74.0)	Reference
Non-Hispanic black	42,619 (18.1)	362 (10.1)	0.6 (0.6 – 0.7)
Hispanic	34,715 (14.7)	411 (11.4)	0.8 (0.7 – 0.8)
Asian/Pacific Islander	12,962 (5.5)	161 (4.5)	0.9 (0.7 – 1.0)
Year of transplantation[d]			
1987 – 1996	54,005 (22.9)	1,269 (35.3)	Reference
1997 – 2002	68,328 (29.0)	1,236 (34.4)	0.9 (0.8 – 1.0)[d]
2003 – 2006	51,878 (22.0)	641 (17.9)	0.9 (0.8 – 1.0)[d]
2007 – 2014	61,564 (26.1)	445 (12.4)	0.9 (0.8 – 1.0)[d]
Transplanted organ			
Kidney	140,987 (59.8)	1,515 (42.2)	Reference
Kidney/pancreas or pancreas	9,792 (4.1)	141 (3.9)	1.7 (1.4 – 2.0)
Liver	43,917 (18.6)	834 (23.2)	1.3 (1.2 – 1.4)
Heart and/or lung	37,725 (16.0)	987 (27.5)	1.8 (1.7 – 2.0)
Other/multiple[e]	3,354 (1.4)	114 (3.2)	3.1 (2.5 – 3.7)
Induction immunosuppression			
No induction	125,213 (53.1)	2,224 (61.9)	Reference
Alemtuzumab	9,078 (3.8)	107 (3.0)	1.4 (1.2 – 1.8)
IL2 receptor antagonists	41,144 (17.5)	456 (12.7)	0.9 (0.8 – 1.1)
Muromonab-CD3	9,822 (4.2)	250 (7.0)	1.3 (1.2 – 1.5)
Polyclonal antibodies	46,053 (19.5)	519 (14.4)	1.0 (0.9 – 1.1)
Multiple induction drugs	4,465 (1.9)	35 (1.0)	0.8 (0.6 – 1.2)
Maintenance immunosuppression[e]			
Cyclosporine/azathioprine	51,603 (21.9)	1,158 (32.3)	Reference
Tacrolimus/mycophenolate mofetil	132,151 (56.0)	1,641 (45.7)	1.1 (1.0 – 1.2)

Characteristics	Solid organ transplant recipients; n (%)	Cases of PTLD[b]; n (%)	aHR (95% CI)[c]
Others	52,021 (22.1)	792 (22.1)	1.0 (0.9 – 1.1)
Maintenance use of mTOR inhibitor[f]			
No	224,203 (95.1)	3,438 (95.7)	Reference
Yes	11,572 (4.9)	153 (4.3)	1.1 (1.0 – 1.3)
Maintenance use of corticosteroids[f]			
No	40,867 (17.3)	518 (14.4)	Reference
Yes	194,908 (82.7)	3,073 (85.6)	0.9 (0.8 – 1.0)
EBV serology status at time of transplantation			
Positive	85,121 (36.1)	739 (20.6)	Reference
Negative	18,741 (8.0)	576 (16.0)	2.7 (2.4 – 3.0)
Missing	131,913 (55.9)	2,276 (63.4)	1.2 (1.1 – 1.3)
Number of HLA mismatches			
0	13,903 (5.9)	153 (4.3)	Reference
1	7,640 (3.2)	112 (3.1)	1.1 (0.9 – 1.4)
2	17,885 (7.6)	244 (6.8)	1.0 (0.8 – 1.2)
3	36,922 (15.7)	492 (13.7)	1.0 (0.8 – 1.2)
4	45,626 (19.3)	714 (19.9)	1.1 (0.9 – 1.4)
5	53,961 (22.9)	814 (22.7)	1.1 (0.9 – 1.3)
6	29,246 (12.4)	456 (12.7)	1.1 (0.9 – 1.4)
Missing	30,592 (13.0)	606 (16.9)	1.0 (0.8 – 1.2)

[a] Recipients were identified from linkage of the SRTR with participating cancer registries, including California (years of cancer registry coverage 1988–2012), Colorado (1988–2009), Connecticut (1973–2009), Florida (1981–2009), Georgia (1995–2010), Hawaii (1973–2007), Illinois (1986–2013), Iowa (1973–2009), Kentucky (1995–2011), Michigan (1985–2009), New Jersey (1979–2010), New York (1976–2010), North Carolina (1990–2010), Pennsylvania (1985–2013), Seattle-Puget sound area of Washington (1974–2014), Texas (1995–2010) and Utah (1973–2008).

[b] Refers to the first occurrence of any type of PTLD in the SRTR or linked cancer registry

[c] aHRs were obtained from Cox regression models with age as the time scale and adjusted for the following variables decided *a priori*: sex, race/ethnicity, year of transplantation, transplanted organ, and time since transplantation (as a time-dependent variable). Follow-up began on the date of first transplantation and ended at the earliest of PTLD diagnosis, graft failure, re-transplantation, loss to follow-up, end of cancer registry coverage or death. aHRs are not presented for age at transplantation because age was used as the time scale. Underlined estimates were considered statistically significant based on two-sided $p < 0.05$.

[d] The aHRs (95%CIs) for the 1997–2002, 2003–2006, and 2007–2014 eras compared to the 1987–1996 era are: 0.91 (0.84–0.98), 0.86 (0.78–0.95) and 0.92 (0.82–1.04), respectively.

[e] Multiple transplanted organs on the same date of transplantation

[f] Maintenance immunosuppression at baseline

Abbreviations: aHR, adjusted hazard ratio; CI, confidence intervals; EBV, Epstein–Barr virus; HLA, human leucocyte antigen; IL2, interleukin-2; mTOR, mechanistic target of rapamycin; PTLD, post-transplant lymphoproliferative disorder; SRTR, US Scientific Registry of Transplant Recipients.