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Risk of lymphoma subtypes after solid organ transplantation in the United States

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Background: Solid organ transplant recipients have high risk of lymphomas, including non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). A gap in our understanding of post-transplant lymphomas involves the spectrum and associated risks of their many histologic subtypes.

Methods: We linked nationwide data on solid organ transplants from the US Scientific Registry of Transplant Recipients (1987–2008) to 14 state and regional cancer registries, yielding 791 281 person-years of follow-up for 19 distinct NHL subtypes and HL. We calculated standardised incidence ratios (SIRs) and used Poisson regression to compare SIRs by recipient age, transplanted organ, and time since transplantation.

Results: The risk varied widely across subtypes, with strong elevations (SIRs 10–100) for hepatosplenic T-cell lymphoma, Burkitt's lymphoma, NK/T-cell lymphoma, diffuse large B-cell lymphoma, and anaplastic large-cell lymphoma (both systemic and primary cutaneous forms). Moderate elevations (SIRs 2–4) were observed for HL and lymphoplasmacytic, peripheral T-cell, and marginal zone lymphomas, but SIRs for indolent lymphoma subtypes were not elevated. Generally, SIRs were highest for younger recipients (<20 years) and those receiving organs other than kidneys.

Conclusion: Transplant recipients experience markedly elevated risk of a distinct spectrum of lymphoma subtypes. These findings support the aetiologic relevance of immunosuppression for certain subtypes and underscore the importance of detailed haematopathologic workup for transplant recipients with suspected lymphoma.

Organ transplantation is a lifesaving option for individuals with end-stage organ disease, and over 28 000 solid organ transplantations are performed yearly in the United States. However, solid organ transplant patients must receive intensive long-term immunosuppressive therapy to prevent rejection of the transplant, putting them at high risk of developing post-transplant lymphoproliferative disorders (PTLDs). These disorders include a spectrum of potentially deadly lymphoid cell proliferations, including non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) (Tsao and Hsi, 2007). The NHL represents one of the most common malignancies diagnosed after transplant (Andreone *et al*, 2003). Risk in transplant recipients is estimated as 3- to 21-fold higher than that in the general population, and perhaps as much as 120-fold higher among children who receive transplants (Kasiske *et al*, 2004; Busnach *et al*, 2006; Caillard *et al*, 2006; Vajdic *et al*, 2006; Giordano *et al*, 2007; Grulich *et al*, 2007; Serraino *et al*, 2007; Jiang *et al*, 2008, 2010; Baccarani *et al*, 2009; Vajdic and van Leeuwen, 2009; Quinlan *et al*, 2010; Engels *et al*, 2011). The NHL risk exhibits a U-shaped pattern over time following transplantation, with risk being highest in the first year after transplant, falling

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subsequently, and then increasing again at 5 or more years after transplant (van Leeuwen *et al*, 2009; Quinlan *et al*, 2011). HL was once considered aetiologically distinct from NHL, but is now recognised as similar to some B-cell NHL subtypes. Risk of HL among transplant recipients is likely lower than that for NHL, having been reported as 2- to 3.6-fold higher than that in the general population (Quinlan *et al*, 2010; Engels *et al*, 2011).

A major gap in our understanding of transplant-related lymphoma involves the spectrum and associated risks of the many histologic subtypes of lymphoma, which are heterogeneous with respect to clinical and epidemiologic characteristics (Morton *et al*, 2006; Swerdlow *et al*, 2008). The two prior studies examining the risk of NHL subtypes among transplant recipients reported substantial elevation in the risk of diffuse large B-cell lymphoma (DLBCL, the most common subtype in most populations) but no increase for follicular lymphoma (another common subtype in the general population) (Quinlan *et al*, 2010; Vajdic *et al*, 2010). These studies were hampered by small numbers, especially of uncommon NHL subtypes, and did not examine how the occurrence of NHL subtypes varied by demographic characteristics or time since transplantation.

Better characterisation of the risk of lymphoma subtypes in transplant recipients would help clinicians caring for these patients, as different subtypes require different management. This information would also improve understanding of the causal importance of immunosuppression. Therefore, we assessed the risks of individual lymphoma subtypes in the recently completed Transplant Cancer Match Study (Engels *et al*, 2011). This large cohort of US solid organ transplant recipients, for whom cancer ascertainment was conducted uniformly via linkage with population-based cancer registries, enabled us to quantify the risks of specific subtypes overall and according to recipient age at transplantation, type of transplanted organ, and time since transplant.

MATERIALS AND METHODS

Transplant cancer match study. The Transplant Cancer Match Study is described in detail elsewhere (http://transplantmatch.cancer.gov) (Engels *et al*, 2011). In brief, the US Scientific Registry of Transplant Recipients (SRTR) was linked with 14 US population-based cancer registries. The SRTR includes structured data regarding all US solid organ transplants occurring since 1987, including recipient demographic characteristics, reason for transplant, and characteristics of the transplanted organs. The cancer registries include standardised information regarding patient demographic characteristics and detailed tumour characteristics.

Serial record linkages were completed between the SRTR and the following central cancer registries, together covering ~42% of the US transplant patient population: California (years of coverage: 1988–2008), Colorado (1988–2006), Connecticut (1973–2006), Georgia (1995–2008), Hawaii (1973–2007), Illinois (1986–2007), Iowa (1973–2007), Michigan (1985–2006), New Jersey (1979–2006), New York (1976–2007), North Carolina (1990–2007), the Seattle-Puget Sound area of Washington State (1974–2008), Texas (1995–2006), and Utah (1973–2008). Record linkages were accomplished using a computer algorithm followed by manual review and confirmation of potential matches. Analyses were restricted to transplant recipients residing in geographic areas covered by the cancer registries during the specified time periods.

The TCM Study was approved by human subjects research review committees at the National Cancer Institute and the following cancer registries: California, Colorado, Connecticut, Georgia, Hawaii, Illinois, Iowa, Michigan, New Jersey, New York, Seattle-Puget Sound, Texas, and Utah. It was formally exempted from human subjects research approval at the Health Resources and Services Administration and the North Carolina cancer registry.

Lymphoma outcomes and follow-up. The NHLs were identified in transplant recipients through linkage with cancer registries. Lymphoma subtypes were classified using International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) site and histology codes according to current International Lymphoma Epidemiology (InterLymph) Consortium consensus guidelines (Turner *et al*, 2010). Transplant recipients were considered at risk of lymphoma beginning at the date of transplantation or the start of cancer registry coverage (whichever came later). Hispanics were followed beginning in 1992 to correspond to the years for which general population rates were available for comparison (see below). Follow-up time ended at the first diagnosis of any lymphoma subtype, death, failure of a transplanted organ, subsequent transplant, loss to follow-up, or last date of cancer registry coverage (whichever came first). Recipients were considered at risk separately during successive transplant episodes. Of the 180 210 distinct transplant episodes, we excluded 1265 because racial/ethnic information was missing or did not correspond to a group for which general population cancer rates were available, and a further 160 episodes occurring among recipients with human immunodeficiency virus (HIV) infection reported to the SRTR. We did not exclude episodes if the recipient had a history of cancer before transplantation. Altogether, our final analytic cohort included 178 785 transplant episodes occurring in 165 734 individuals, 1617 NHL, and 48 HL cases.

Statistical analysis. For each lymphoma subtype, we measured the risk in transplant recipients relative to the general population using the standardised incidence ratio (SIR, i.e., observed/expected number of cases). Observed numbers were derived from the cancer registry linkages, as described above. Expected numbers were calculated by applying general population cancer incidence rates obtained from each cancer registry to person-time at risk among transplant recipients, stratified by sex, 5-year age group, race/ethnicity, and calendar year. Rates for whites, blacks, and Asians/Pacific Islanders were derived from participating registries. Rates for Hispanics (available 1992 onward) were derived from the US Surveillance, Epidemiology, and End Results programme, in which 8 of the 14 contributing cancer registries participate. The 95% confidence intervals (CIs) around each SIR were derived assuming that the observed counts follow a Poisson distribution.

We also calculated SIRs and 95% CIs across categories defined by age at transplant, transplanted organ, and successive time intervals (1–360 days, 361–1800 days, and 1801+ days) after transplant. Univariate Poisson regression models were created for each subtype and used to test for heterogeneity across these categories.

In sensitivity analyses we (1) excluded all transplants for which the reported NHL was not the first haematologic malignancy reported, and (2) excluded transplants for which there was a gap between date of transplant and the beginning of cancer registry coverage. Results from these sensitivity analyses were similar to those from our main analysis and thus are not presented here. All CIs and statistical tests were two sided.

RESULTS

We evaluated 178 785 solid organ transplants in 165 734 individuals, with 791 281 person-years of follow-up. Table 1 describes the demographic characteristics of individuals who received these transplants. Of the transplant recipients, 61% were male, and the median age at transplant was 47.0 years, with a quarter of patients under age 35 years at the time of transplant. Recipients were racially

Table 1. Characteristics of 178,785 solid organ transplants*, United States, 1987–2008

Characteristic	*n* (%)
Sex	
Male	108 805 (60.86)
Female	69 980 (39.14)
Age at transplant, years	
0–19	16 130 (9.02)
20–34	28 128 (15.73)
35–49	56 700 (31.71)
50–64	63 798 (35.68)
65 +	14 029 (7.85)
Race/ethnicity	
White, non-Hispanic	109 702 (61.36)
Black, non-Hispanic	29 868 (16.71)
Hispanic	28 446 (15.91)
Asian/Pacific Islander	10 769 (6.02)
Transplanted organ	
Kidney	104 466 (58.43)
Pancreas or kidney and pancreas	7 991 (4.47)
Liver	38 473 (21.52)
Heart and/or lung	25 449 (14.23)
Other or multiple	2406 (1.35)
Transplant number	
First	163 071 (91.21)
Second	14 404 (8.06)
Third or higher	1310 (0.73)
Calendar year of transplant	
1987–1994	35 280 (19.73)
1995–1999	46 890 (26.23)
2000–2004	57 801 (32.33)
2005–2008	38 814 (21.71)

*Includes 178,785 solid organ transplant episodes occurring in 165,734 recipients.

and ethnically diverse, with almost 40% of patients being non-white. Kidney transplants were most common, but 41% of transplants were of other organs, and 91% were first transplants.

Through matches with cancer registry records, 1617 NHL diagnoses and 48 HL diagnoses among transplant recipients were identified. Of the NHLs, specific histologic subtype was reported for 1285 (80%). Compared with cases with specified subtypes, NHLs for which histologic subtype was not reported (i.e., 'NHL, not otherwise specified') were similar in terms of age, sex, and organ transplanted, but were significantly ($P<0.05$) more likely to have disease limited to lymph nodes (i.e., nodal) and to have been diagnosed in the earlier years of the study (e.g., 1987–1994).

Overall, transplant recipients had over six-fold increased risk of developing any kind of NHL compared with the general population (SIR = 6.2, 95% CI: 5.9–6.5). Table 2 describes the risk for 19 defined distinct NHL subtypes. Among NHLs for which specific subtypes were reported, 85.5% were B-cell lymphomas and 6.2% were T-cell lymphomas. The NHL subtype with the highest elevation in risk was hepatosplenic T-cell lymphoma, an uncommon NHL subtype for which the risk was elevated 100-fold (SIR = 100, 95% CI: 33–234) above the general population. However, this increase was based on only six cases and an incidence rate of less than one per 100 000 person-years. The most common subtype diagnosed was DLBCL, which comprised almost two-thirds of all post-transplant NHLs with specified subtype, and for which the risk was over 13 times higher than in the general population (SIR = 13.5, 95% CI: 12.7–14.4). After DLBCL, the next most commonly diagnosed subtype was Burkitt's lymphoma, for which the risk was ~25 times elevated (SIR = 24.5, 95% CI: 19.6–30.2). Other B-cell lymphomas with significantly elevated risks included lymphoplasmacytic lymphoma (SIR = 2.8, 95% CI: 1.6–4.5) and marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT; SIR = 2.8, 95% CI: 1.9–4.0). The risk of developing HL was significantly elevated 3.6-fold (SIR = 3.6, 95% CI: 2.9–4.4) compared with the general population.

When T-cell lymphomas were considered as a single entity, the risk was seven-fold higher than in the general population (SIR = 7.1, 95% CI: 5.6–8.9; Table 2). Peripheral T-cell lymphomas and anaplastic large-cell lymphomas comprised over 80% of the T-cell lymphomas, with other subtypes occurring rarely. Among the T-cell lymphomas, the greatest risk elevation was for hepatosplenic T-cell lymphoma (SIR = 100, as noted above). Other T-cell lymphomas with elevated risks included extranodal natural killer (NK)/T-cell lymphomas, nasal type (SIR = 15.0, 95% CI: 6.5–29.6), anaplastic large-cell lymphoma (SIR = 12.8, 95% CI: 9.0–17.7), primary cutaneous anaplastic large-cell lymphoma (SIR = 13.5, 95% CI: 6.2–25.5), and other peripheral T-cell lymphomas (SIR = 3.9, 95% CI: 2.7–5).

Among other specified NHLs, the risk was also elevated for precursor B- or T-cell lymphoblastic leukaemia/lymphoma, compared with the general population (SIR = 2.0, 95% CI: 1.23–3.20). In sharp contrast, few cases and no significant elevations in risk were observed for follicular lymphoma, small lymphocytic lymphoma/chronic lymphocytic leukaemia (CLL/SLL), mantle cell lymphoma, or mycosis fungoides/Sézary's syndrome.

The risks differed substantially according to the age at transplant, with a strong inverse relationship between SIRs and age demonstrated for several NHL subtypes and HL (Table 3). Among recipients aged <20 years at the time of transplantation, the risks were strikingly elevated for Burkitt's lymphoma (SIR = 123, 95% CI: 79.0–183), DLBCL (SIR = 379, 95% CI: 318–447), peripheral T-cell lymphoma (SIR = 172, 95% CI: 69.1–354), and anaplastic large-cell lymphoma (SIR = 96.9, 95% CI: 41.8–191). For many subtypes, it was difficult to assess gradients in risk by age because there were fewer than three cases diagnosed among those aged <20 years at transplant. Notably, however, the risks for most subtypes among individuals aged ≥50 years at the time of transplantation remained elevated compared with the general population.

Table 4 shows that for some subtypes, the patterns of risk also differed with respect to time since transplant, although for other subtypes, the numbers were small and differences were not significant. The SIRs for DLBCL and anaplastic large-cell lymphoma showed a U-shaped pattern, with risks highest in the first year after transplant, lower at 361–1800 days after transplant, and slightly higher again 1801 + days after transplant. In contrast, SIRs for HL, Burkitt's lymphoma, peripheral T-cell lymphomas, and hepatosplenic T-cell lymphoma were not statistically significantly elevated in the first year after transplant but increased subsequently, with markedly elevated relative risk observed 1801 + days after transplant.

The risk of lymphoma subtypes differed by the type of organ transplanted (Table 5). For most subtypes, kidney recipients had lower SIRs than liver or thoracic organ (heart and/or lung) recipients (although still elevated compared with the general population in many instances). However, the number of cases for many subtypes was small, and risk did not differ significantly by organ. The risks for DLBCL and anaplastic large-cell lymphoma were highest among pancreas and kidney/pancreas recipients, whereas Burkitt's lymphoma risk was highest among liver and

Table 2. Overall SIRs for lymphoma subtypes among solid organ transplant recipients, United States, 1987–2008

	ICD-O-3 site and histology codes	Observed count	SIR	95% CI	Incidence rate / 100 000 person-years
B-cell lymphoma subtype					
Burkitt's lymphoma/leukaemia	9687, 9826	88	**24.5**	**19.7–30.2**	11.1
Chronic lymphocytic lymphoma/ small lymphocytic lymphoma	9670, 9823	36	**0.7**	**0.5–0.9**	4.5
Diffuse large B-cell lymphoma	9678–9680, 9684	948	**13.5**	**12.7–14.4**	119.8
Follicular lymphoma	9690, 9691, 9695, 9698	38	0.9	0.7–1.3	4.8
Lymphoplasmacytic lymphoma	9671, 9761	16	**2.8**	**1.6–4.5**	2.0
Mantle cell	9673	3	0.4	0.1–1.0	0.4
Marginal zone	9689, 9699, 9760, 9764, 9699, 9715	35	**2.2**	**1.6–3.1**	4.4
Splenic/nodal marginal zone	9689, 9699 (site 77.0–77.9), 9715 (site 77.0–77.9)	6	1.1	0.4–2.4	0.8
MALT type	9760, 9764, 9699 (excl site 77.0–77.9), 9715 (excl site 77.0–77.9)	29	**2.8**	**1.9–4.0**	3.7
T-cell lymphoma subtype					
Peripheral T-cell lymphoma	9702, 9705, 9708, 9709, 9717	30	**3.9**	**2.7–5.6**	3.8
ALCL	9714	36	**12.8**	**9.0–17.7**	4.5
Primary cutaneous ALCL	9718	9	**13.5**	**6.2–25.5**	1.1
Mycosis fungoides/Sézary's syndrome	9700, 9701	8	1.6	0.7–3.2	1.0
Hepatosplenic T-cell lymphoma	9716	5	**100**	**33–234**	0.6
NK/T-cell lymphoma	9719	8	**15.0**	**6.5–29.6**	1.0
All T-cell lymphoma combined	9702–9718	80	**7.1**	**5.7–8.9**	10.1
Precursor B- or T-cell lymphoblastic leukaemia/lymphoma	9727–9729, 9835–9837	19	**2.0**	**1.2–3.2**	2.4
NHL, other	9762, 9827, 9831–9834, 9940, 9948	9	1.7	0.8–3.3	1.1
NHL, not otherwise specified	9590–9595, 9675, 9820, 9970	332	**10.2**	**9.1–11.3**	42.0
All NHL	9590–9595, 9670, 9671, 9673, 9675, 9678–9680, 9684, 9687, 9689, 9690, 9691, 9695, 9698, 9699, 9700, 9701, 9702, 9705, 9708, 9709, 9714, 9715, 9716, 9717, 9718, 9719, 9727–9729, 9760, 9761, 9762, 9764, 9820, 9823, 9826, 9827, 9831–9837, 9940, 9948, 9970	1617	**6.2**	**5.9–6.5**	204.4
Hodgkin's lymphoma					
(excluding nodular lymphocyte predominant type)	9650–9655, 9661–9665, 9667	83	**3.6**	**2.9–4.4**	10.5

Abbreviations: ALCL = anaplastic large-cell lymphoma; CI = confidence interval; ICD-O-3 = International Classification of Diseases for Oncology, 3rd edition; MALT = mucosa-associated lymphoid tissue; NHL = non-Hodgkin's lymphoma; NK = natural killer; SIR = standardised incidence ratio. Bold indicates SIRs significantly different from 1 at $P<0.05$.

thoracic organ recipients. None of the recipients who developed hepatosplenic T-cell lymphoma received a liver transplant, rather, four of the six recipients received kidneys.

The patterns for NHL overall according to age, organ type, and time since transplant generally mirrored those observed for DLBCL, the most common subtype (Tables 3–5). Similarly, the patterns of risk of unclassified lymphoma (NHL, not otherwise specified) were also similar to those observed for DLBCL.

DISCUSSION

Non-Hodgkin's lymphoma is among the most common malignancies diagnosed among solid organ transplant recipients. Overall, the risk for NHL is six-fold higher following transplantation than in the general population, but in this large, population-based study we demonstrate that the risks vary dramatically by lymphoma subtype. Elevated risks were particularly striking (>10-fold) for hepatosplenic T-cell lymphoma, Burkitt's lymphoma, extranodal NK/T-cell lymphoma nasal type, DLBCL, and anaplastic large-cell lymphoma (both systemic and primary cutaneous forms). For DLBCL and Burkitt's lymphoma, which were the most common lymphoma subtypes after transplant, the relative risks were most strongly pronounced among transplant patients under age 20 years, and differed according to the type of organ transplanted. We also observed moderately elevated risks (i.e., 2- to 3-fold higher than the general population) for HL, lymphoplasmacytic lymphomas, precursor B- or T-cell lymphoblastic leukaemia/lymphoma, other T-cell lymphomas, and marginal zone lymphoma of MALT type, whereas the risks were not increased for follicular or mantle cell lymphomas, CLL/SLL, or mycosis fungoides/Sézary's syndrome.

The mechanisms explaining the different spectrum of lymphoma subtypes among transplant patients compared with the general population include immunosuppression, including the early, intense induction phase and the later maintenance phase; chronic immune activation because of the presence of donor organ tissue; or the combined effects of these, resulting in long-term, chronic immune dysfunction. The lymphoma subtypes for which the risk is elevated are similar to those that are increased in HIV-infected patients (Mbulaiteye *et al*, 2003; Biggar *et al*, 2007;

Table 3. SIRs and 95% CIs for development of lymphoma subtypes in subgroups of solid organ transplant recipients by age at transplant year, United States, 1987–2008

	Age at transplant year															
	0–19			20–34			35–49			50–64			65+			Poisson
Subtype	*n*	SIR	95% CI	*n*	SIR	95% CI	*n*	SIR	95% CI	*n*	SIR	95% CI	*n*	SIR	95% CI	*P*-value*
B-cell lymphoma subtype																
Burkitt's lymphoma/leukaemia	24	**123**	**79–183**	16	**39.7**	**22.7–64.4**	21	**17.7**	**10.9–27.0**	24	**16.7**	**10.7–24.9**	3	**8.1**	**1.7–23.8**	**<0.0001**
Chronic lymphocytic lymphoma /small lymphocytic lymphoma	<3	**77.2**	**2.0–430.2**	<3	2.4	0.1–13.6	5	0.6	0.2–1.5	23	0.7	0.4–1.0	6	0.5	0.2–1.0	0.05
Diffuse large B-cell lymphoma	138	**379**	**318–447**	135	**40.3**	**33.8–47.7**	249	**15.6**	**13.7–17.6**	348	**9.4**	**8.4–10.5**	78	**5.8**	**4.6–7.3**	**<0.0001**
Follicular lymphoma	<3	**36.6**	**4.4–132**	4	3.4	0.9–8.8	8	0.8	0.4–1.6	20	0.9	0.5–1.4	4	0.6	0.2–1.6	**0.0025**
Lymphoplasmacytic lymphoma	0	0.0	0–1124	0	0.0	0.0–55.9	3	3.5	0.7–10.3	8	**2.4**	**1.0–4.7**	5	**3.5**	**1.1–8.1**	0.91
Mantle cell	0	0.0	0–2583	0	0.0	0.0–52.4	0	0.0	0.0–2.7	<3	0.4	0.1–1.4	<3	0.5	0.0–3.1	–
Marginal zone	0	0.0	0–111	5	**12.8**	**4.2–29.9**	13	**4.1**	**2.2–7.1**	9	1.0	0.5–1.9	8	**2.5**	**1.1–4.9**	**0.0003**
Splenic/nodal marginal zone	0	0.0	0–463	3	**30.7**	**6.3–89.8**	<3	1.0	0.0–5.7	<3	0.3	0.0–1.8	<3	0.8	0.0–4.7	**0.0022**
MALT type	0	0.0	0–147	<3	6.8	0.8–24.7	12	**5.5**	**2.9–9.7**	8	1.4	0.6–2.7	7	**3.5**	**1.4–7.1**	**0.02**
T-cell lymphoma subtype																
Peripheral T-cell lymphoma	7	**172**	**69–354**	4	**12.9**	**3.5–33.1**	6	**3.5**	**1.3–7.7**	9	**2.1**	**1.0–4.1**	4	2.9	0.8–7.5	**<0.0001**
ALCL	8	**96.9**	**41.8–191**	6	**27.7**	**10.2–60.4**	8	**10.8**	**4.7–21.4**	14	**10.1**	**5.5–17.0**	0	0.0	0.0–9.3	**<0.0001**
Primary cutaneous ALCL	<3	**127**	**3–706**	0	0.0	0.0–114.6	<3	**12.7**	**1.5–45.9**	4	**11.2**	**3.1–28.7**	<3	**17.5**	**2.1–63.4**	0.43
Mycosis fungoides/ Sézary's syndrome	<3	33.3	0.8–185	0	0.0	0.0–14.2	4	3.1	0.8–7.9	<3	0.8	0.1–2.8	<3	1.4	0.0–7.6	0.10
Hepatosplenic T-cell lymphoma	<3	**269**	**7–1501**	0	0.0	0.0–387.7	<3	**109**	**13–393**	<3	**131**	**16–472**	0	0.0	0.0–1256.2	0.50
NK/TCL, nasal type	0	0.0	0–316.0	<3	17.4	0.4–96.9	<3	6.2	0.2–34.6	6	**25.9**	**9.5–56.5**	0	0.0	0.0–52.2	0.28
All T-cell lymphoma	17	**126**	**73–202**	10	**17.5**	**8.4–32.2**	18	**6.8**	**4.0–10.8**	29	**4.8**	**3.2–6.9**	6	**3.2**	**1.2–6.9**	**<0.0001**
Precursor B- or T- cell lymphoblastic leukaemia/lymphoma	7	**3.2**	**1.3–6.6**	3	3.0	0.6–8.6	4	1.9	0.5–4.8	5	1.6	0.5–3.7	0	0.0	0.0–4.8	0.27
NHL, other	<3	**79.0**	**2.0–440**	<3	4.9	0.1–27.5	3	2.0	0.4–5.9	4	1.4	0.4–3.7	0	0.0	0.0–4.8	0.05
NHL, not otherwise specified	39	**266**	**189–363**	40	**26.3**	**18.8–35.8**	93	**13.0**	**10.5–15.9**	132	**7.6**	**6.4–9.0**	28	**4.4**	**2.9–6.4**	**<0.0001**
All NHL	230	**72.1**	**63.1–82.1**	216	**22.8**	**19.9–26.1**	422	**7.7**	**7.0–8.5**	609	**4.2**	**3.9–4.6**	140	**2.8**	**2.4–3.3**	**<0.0001**
Hodgkin's lymphoma	20	**14.1**	**8.6–21.8**	16	**3.6**	**2.0–5.8**	21	**3.0**	**1.9–4.6**	24	**2.9**	**1.9–4.3**	<3	1.0	0.1–3.5	**<0.0001**

Abbreviations: ALCL = anaplastic large-cell lymphoma; CI = confidence interval; MALT = mucosa-associated lymphoid tissue; NHL = non-Hodgkin's lymphoma; NK = natural killer; SIR = standardised incidence ratio; TCL = T-cell lymphoma. *P-value from univariate Poisson regression testing for heterogeneity across categories. '–' Indicates too few cases to estimate heterogeneity. Bold indicates SIRs significantly different from 1 at $P<0.05$.

Engels *et al*, 2008; Vajdic *et al*, 2010), another population experiencing both chronic immunosuppression and immune activation. Investigators in the United States and Australia have demonstrated especially elevated risks among HIV-infected individuals for 'high-grade' NHL subtypes as a group (SIR ~50–110) and for DLBCL (SIRs 25–100), Burkitt's lymphoma (SIRs 50–140), and T-cell lymphomas (SIR ~15) (Mbulaiteye *et al*, 2003; Engels *et al*, 2006; van Leeuwen *et al*, 2009; Vajdic *et al*, 2010). In contrast, follicular or 'low-grade' lymphoma risks were not higher than in the general population in any of the transplant or HIV-infected groups (Mbulaiteye *et al*, 2003; Quinlan *et al*, 2010; Vajdic *et al*, 2010). The overall relative risks observed here are lower than those observed in HIV-infected populations, perhaps because of the different pattern of immunosuppression or the different type of immune stimulus conferred by a donor organ than associated with HIV infection.

These data are informative with regard to several aspects of lymphomagenesis for specific subtypes. For DLBCL, our observations are consistent with the known role of Epstein–Barr virus (EBV)-driven B-cell expansion under conditions of intense immunosuppression, especially in children. Epstein–Barr virus is detected in the tumour cells of most transplant-related DLBCLs (Carbone *et al*, 2009). We found that the risk of developing DLBCL was concentrated in children (ages 0–19 years), and was highest in the first year after transplant. These findings agree with previous reports of transplant-related NHL overall and PTLD (Opelz *et al*, 2009; Vajdic and van Leeuwen, 2009) and are expected, given that DLBCL comprises a large fraction of PTLD. Children are often EBV seronegative at transplantation, which puts them at risk of subsequent primary EBV infection and PTLD (Jenson, 2011; Quinlan *et al*, 2011). For Burkitt's lymphoma, which is also an aggressive lymphoma, the risk was similarly highest in children, but was not elevated in the first year after transplant and rose with time since transplant. Of interest, only 40–60% of HIV-associated Burkitt's lymphoma is EBV related (Carbone *et al*, 2009). We were unable to separate EBV-defined cases, and it is possible that the age and latency patterns that we observed reflect mixed occurrence for EBV-positive and -negative forms of Burkitt's lymphoma after transplant (Carbone *et al*, 2009). Transplant-related cases of HL are also commonly EBV positive (Bierman *et al*, 1996; Knight *et al*, 2009), and in our study, HL risk also increased with time since transplant.

We also observed statistically significantly elevated risks of marginal zone lymphomas of MALT type and lymphoplasmacytic lymphoma, although the magnitudes of elevation were lower than those for DLBCL and Burkitt's lymphoma. Outside of the transplant setting, these subtypes are thought to arise under conditions of persistent immune stimulation by chronic microbial infections (e.g., *Helicobacter pylori* for gastric MALT type lymphoma, hepatitis C virus for lymphoplasmacytic lymphoma) (Engels, 2007; Giordano *et al*, 2007; de Sanjose *et al*, 2008). Transplant-related immunosuppression may increase microbial activity or modulate the immune response against these micro-organisms. In contrast, for other indolent B-cell lymphomas such as follicular lymphoma and CLL/SLL, our data are not suggestive of major roles for the types of immunosuppression, immune

Table 4. SIRs and 95% CIs for development of lymphoma subtypes in subgroups of solid organ transplant recipients by time since transplant, United States, 1987–2008

	Time since transplant									
	1–360 days			361–1800 days			1801 + days			Poisson
Subtype	*n*	SIR	95% CI	*n*	SIR	95% CI	*n*	SIR	95% CI	*P*-value*
B-cell lymphoma subtype										
Burkitt's lymphoma/leukaemia	<3	3.3	0.4–11.8	54	**31.7**	**23.8–41.3**	32	**25.0**	**17.1–35.3**	**<0.0001**
Chronic lymphocytic lymphoma/small lymphocytic lymphoma	11	1.4	0.7–2.4	12	0.5	0.3–0.9	13	0.6	0.3–1.0	0.05
Diffuse large B-cell lymphoma	335	**30.1**	**26.9–33.5**	305	**9.4**	**8.4–10.5**	308	**11.6**	**10.4–13.0**	**<0.0001**
Follicular lymphoma	13	**2.1**	**1.1–3.5**	8	0.4	0.2–0.9	17	1.1	0.6–1.8	**0.0014**
Lymphoplasmacytic lymphoma	3	3.5	0.7–10.4	6	2.3	0.9–5.1	7	**3.0**	**1.2–6.2**	0.81
Mantle cell	<3	0.8	0.0–4.7	<3	0.3	0.0–1.5	<3	0.3	0.0–1.6	0.71
Marginal zone	6	**2.7**	**1.0–5.9**	13	**1.9**	**1.0–3.2**	16	**2.4**	**1.4–3.9**	0.69
Splenic/nodal marginal zone	<3	1.3	0.0–7.5	<3	0.4	0.0–2.4	4	1.7	0.5–4.4	0.38
MALT type	5	**3.4**	**1.1–7.9**	12	**2.6**	**1.4–4.6**	12	**2.8**	**1.5–4.9**	0.89
T-cell lymphoma subtype										
Peripheral T-cell lymphoma	<3	1.7	0.2–6.2	11	**3.2**	**1.6–5.7**	17	**5.7**	**3.3–9.1**	0.11
ALCL	15	**32.8**	**18.4–54.1**	5	**3.7**	**1.2–8.7**	16	**15.6**	**8.9–25.4**	**<0.0001**
Primary cutaneous ALCL	3	**32.4**	**6.7–94.7**	<3	3.5	0.1–19.6	5	**17.1**	**5.6–40.0**	0.08
Mycosis fungoides/Sézary's syndrome	<3	2.4	0.3–8.7	<3	0.8	0.1–3.1	4	2.3	0.6–5.8	0.42
Hepatosplenic T-cell lymphoma	0	0.0	0.0–451.4	<3	**42.7**	**1.1–238.0**	4	**219**	**60–560**	0.10
NK/TCL, nasal type	<3	11.9	0.3–66.33	3	**12.3**	**2.6–36.1**	4	**19.4**	**5.3–48.6**	0.81
All T-cell lymphoma	20	**11.5**	**7.0–17.8**	18	**3.5**	**2.1–5.5**	42	**9.7**	**7.0–13.1**	**<0.0001**
Precursor B- or T-cell lymphoblastic leukaemia/lymphoma	<3	1.2	0.1–4.2	11	**2.4**	**1.2–4.3**	6	2.0	0.7–4.3	0.59
NHL, other	0	0.0	0.0–4.3	5	2.0	0.7–4.7	4	2.1	0.6–5.4	0.20
NHL, not otherwise specified	115	**20.2**	**16.7–24.3**	124	**7.8**	**6.5–9.3**	93	**8.4**	**6.8–10.3**	**<0.0001**
All NHL	511	**12.4**	**11.3–13.5**	561	**4.6**	**4.3–5.0**	545	**5.5**	**5.0–6.0**	**<0.0001**
Hodgkin's lymphoma	6	1.4	0.5–3.1	36	**3.2**	**2.2–4.4**	41	**5.4**	**3.9–7.3**	**0.001**

Abbreviations: ALCL = anaplastic large-cell lymphoma; CI = confidence interval; MALT = mucosa-associated lymphoid tissue; NHL = non-Hodgkin's lymphoma; NK = natural killer; SIR = standardised incidence ratio; TCL = T-cell lymphoma. **P*-value from univariate Poisson regression testing for heterogeneity across categories. Bold indicates SIRs significantly different from 1 at $P<0.05$.

activation, or other immune disturbances experienced by transplant recipients.

Although T-cell lymphomas constituted a small proportion of NHLs in this transplant population, we observed very high relative risks of certain T-cell subtypes, including hepatosplenic T-cell lymphoma and both systemic and primary cutaneous anaplastic large-cell lymphomas. For anaplastic large-cell lymphoma, relative risks were markedly elevated in the first year after transplant. Of interest, EBV is not generally thought to play an important role in the aetiology of T-cell PTLD (Engels, 2007). Although the exceedingly rare hepatosplenic T-cell lymphoma is well recognised as a type of PTLD, EBV is infrequently detected in tumour cells of this malignancy (Engels, 2007). The very high relative risks of hepatosplenic T-cell and anaplastic large-cell lymphomas observed here after transplant, but not in HIV-infected individuals (Opelz and Dohler, 2004; LaCasce, 2006), may suggest that unique aspects of transplant-associated immune disturbance are aetiologically important. Inflammatory and anti-inflammatory activity are of interest because of the apparent association of hepatosplenic T-cell lymphomas with use of tumour necrosis factor-α (TNF-α) inhibitors for Crohn's disease, arthritis, and other autoimmune diseases (Hellgren *et al*, 2010; Deepak *et al*, 2013; Mason and Siegel, 2013). It is also interesting that none of the hepatosplenic T-cell lymphomas occurred in liver recipients, among whom the donor organ provides a strong and sustained local immune stimulus.

Our data also demonstrate substantial variation in the risk of lymphoma subtypes according to age and time since transplant. In general, SIRs for most lymphoma subtypes were elevated among young transplant recipients. This pattern probably reflects the contribution of primary EBV infection in younger recipients, as well as a countervailing age-related rise in NHL incidence in the general population due to other mechanisms. Although we confirmed a U-shaped pattern in overall NHL risk over time, a pattern previously observed by others (van Leeuwen *et al*, 2009; Quinlan *et al*, 2011), we did not find a consistent pattern of risk across all the specific subtypes. Intense, T cell-depleting induction immunosuppressive agents used at the time of transplantation may explain why the relative risks of DLBCL and systemic and cutaneous anaplastic large-cell lymphoma were highest nearer the time of transplant. In contrast, the relative risk of Burkitt's lymphoma increased with longer time since transplant. Among older recipients and among recipients many years post transplant, lymphoma occurrence may be caused by some combination of age-related immune senescence, immunosuppression-related immune dysfunction, and chronic antigenic stimulation from the transplanted graft or infection (Opelz and Dohler, 2004; Vajdic and van Leeuwen, 2009; van Leeuwen *et al*, 2009).

Our analysis is the first to assess lymphoma subtype occurrence by the type of organ transplanted. The relative risk of DLBCL was substantially higher among pancreas and pancreas/kidney recipients than recipients of other organs, and Burkitt's lymphoma risk was highest among recipients of liver and thoracic organ (heart and/or lung) transplants. Most prior studies of post-transplant cancer risk have focussed on kidney recipients, but some have reported higher risks of overall NHL for small intestine or lung recipients than heart, liver, or kidney recipients (LaCasce, 2006; Tsao and Hsi, 2007). In the Collaborative Transplant Study, PTLD

Table 5. SIRs and 95% CIs for development of lymphoma subtypes in subgroups of solid organ transplant recipients by transplanted organ, United States, 1987–2008

	Transplanted organ															
	Kidney			Pancreas or kidney and pancreas			Liver			Heart and/or lung			Other or multiple			Poisson
Subtype	*n*	SIR	95% CI	*n*	SIR	95% CI	*n*	SIR	95% CI	*n*	SIR	95% CI	*n*	SIR	95% CI	*P*-value*
B-cell lymphoma subtype																
Burkitt's lymphoma/leukaemia	29	**14.4**	**9.7–20.7**	<3	7.4	0.2–41.1	38	**47.1**	**33.3–64.6**	20	**33.0**	**20.2–51.0**	0	0.0	0.0–116.0	**<0.0001**
Chronic lymphocytic lymphoma/small lymphocytic lymphoma	18	0.7	0.4–1.1	0	0.0	0.0–4.4	10	0.8	0.4–1.5	8	0.6	0.3–1.2	0	0.0	0.0–8.5	0.73
Diffuse large B-cell lymphoma	411	**11.0**	**9.9–12.1**	**55**	**32.6**	**24.6–42.5**	215	**13.1**	**11.4–15.0**	254	**18.2**	**16.0–20.6**	13	**22.5**	**12.0–38.5**	**<0.0001**
Follicular lymphoma	17	0.8	0.5–1.3	0	0.0	0.0–3.5	15	1.5	0.8–2.5	6	0.7	0.3–1.6	0	0.0	0.0–10.6	0.18
Lymphoplasmacytic lymphoma	10	**3.5**	**1.7–6.4**	0	0.0	0.0–42.4	<3	0.7	0.0–4.1	5	**3.7**	**1.2–8.6**	0	0.0	0.0–79.4	0.34
Mantle cell	<3	0.5	0.1–1.8	0	0.0	0.0–24.1	<3	0.5	0.0–2.7	0	0.0	0.0–1.8	0	0.0	0.0–49.0	0.76
Marginal zone	16	**1.9**	**1.1–3.1**	<3	3.0	0.1–16.6	12	**3.1**	**1.6–5.4**	5	1.7	0.5–3.9	<3	7.2	0.2–40.1	0.54
Splenic/nodal marginal zone	4	1.4	0.4–3.6	0	0.0	0.0–34.6	0	0.0	0.0–2.7	<3	1.8	0.2–6.5	0	0.0	0.0–73.5	0.41
MALT type	12	**2.2**	**1.1–3.8**	<3	4.4	0.1–24.4	12	**4.8**	**2.5–8.4**	3	1.6	0.3–4.6	<3	11.3	0.3–62.7	0.16
T-cell lymphoma subtype																
Peripheral T-cell lymphoma	15	**3.6**	**2.0–5.9**	<3	5.7	0.1–31.7	8	**4.7**	**2.0–9.3**	6	**4.1**	**1.5–8.9**	0	0.0	0.0–55.8	0.90
ALCL	14	**9.2**	**5.0–15.4**	<3	**24.0**	**2.9–86.7**	9	**14.4**	**6.6–27.3**	10	18.1	8.7–33.2	<3	**42.9**	**1.1–239.2**	0.33
Primary cutaneous ALCL	4	**11.3**	**3.1–28.9**	0	0.0	0.0–190.2	3	**19.2**	**4.0–56.1**	<3	**15.1**	**1.8–54.4**	0	0.0	0.0–572.4	0.88
Mycosis fungoides/Sézary's syndrome	<3	0.7	0.1–2.6	<3	8.2	0.2–45.7	3	2.8	0.6–8.2	<3	2.0	0.3–7.4	0	0.0	0.0–93.1	0.37
Hepatosplenic T-cell lymphoma	4	**131**	**36–334**	0	0.0	0.0–1753.0	<3	**109**	**3–608**	0	0.0	0.0–481.6	0	0.0	0.0–12027.9	–
NK/TCL, nasal type	6	**19.5**	**7.1–42.4**	0	0.0	0.0–216.0	0	0.0	0.0–31.2	<3	**23.9**	**2.9–86.3**	0	0.0	0.0–725.5	–
All T-cell lymphoma	37	**6.0**	**4.2–8.3**	3	**10.6**	**2.2–31.1**	21	**8.4**	**5.2–12.8**	18	**8.2**	**4.9–13.0**	<3	10.4	0.3–57.7	0.63
Precursor B- or T-cell lymphoblastic leukaemia/lymphoma	7	1.4	0.6–3.0	0	0.0	0.0–14.3	7	2.9	1.2–6.0	4	2.4	0.7–6.3	<3	8.8	0.2–49.0	0.36
NHL, other	4	1.5	0.4–3.8	<3	6.2	0.2–34.7	<3	0.8	0.0–4.6	3	2.7	0.6–7.8	0	0.0	0.0–84.1	0.64
NHL, not otherwise specified	126	**7.3**	**6.1–8.7**	22	**32.0**	**20.1–48.5**	76	**10.3**	**8.1–12.8**	102	**14.6**	**11.9–17.7**	6	**25.8**	**9.5–56.2**	**<0.0001**
All NHL	684	**5.0**	**4.6–5.4**	84	**14.4**	**11.5–17.9**	398	**6.4**	**5.8–7.1**	429	**7.7**	**7.0–8.5**	22	**10.1**	**6.3–15.3**	**<0.0001**
Hodgkin's lymphoma	48	**3.6**	**2.6–4.7**	<3	**2.0**	**0.2–7.2**	14	**3.0**	**1.6–5.0**	18	**4.7**	**2.8–7.4**	<3	5.5	0.1–30.9	0.61

Abbreviations: ALCL = anaplastic large-cell lymphoma; CI = confidence interval; MALT = mucosa-associated lymphoid tissue; NHL = non-Hodgkin's lymphoma; NK = natural killer; SIR = standardised incidence ratio; TCL = T-cell lymphoma. **P*-value from univariate Poisson regression testing for heterogeneity across categories. '–' Indicates too few cases to estimate heterogeneity.

risk was substantially higher among heart/lung and lung recipients than among other recipients (Opelz and Dohler, 2004). Variation in the risk of DLBCL and other subtypes by organ type may relate to differences in immunosuppressive regimens or the intensity of immunosuppression. Along these lines, some studies have shown that overall NHL risk is higher with certain induction immunosuppression agents, particularly monoclonal anti-CD3 antibody (Bustami *et al*, 2004; Dharnidharka *et al*, 2012). Among HIV-infected patients, the risk of DLBCL also has been shown to correlate with the degree of immunosuppression as reflected by CD4 count (Biggar *et al*, 2007). Alternatively, it is possible that different transplanted organs confer different levels of chronic antigen stimulation relevant to lymphomagenesis.

Although DLBCL is the most commonly diagnosed B-cell malignancy in the general population, it represents only 25–30% of all NHL cases (Morton *et al*, 2006), whereas it comprises over half of all transplant-related NHLs. Follicular lymphoma and CLL/SLL each comprise ~15–20% of NHLs diagnosed in the general population, but <3% of NHL cases in our transplant cohort. Notably, transplant recipients thus have higher proportions of aggressive subtypes and lower proportions of indolent B-cell lymphomas. Because many of the subtypes with elevated risk are rare in the general population, our results underscore the importance of expert haematopathologic workup of suspicious lymphoproliferations among transplant patients (Jagadeesh *et al*, 2012) and, moreover, suggest a specific range of lymphoma subtypes as differential diagnoses among such patients. Correct diagnosis of subtype is important for management of post-transplant lymphoma, most importantly for planning therapeutic regimen, which varies substantially by specific lymphoma subtype.

This study has several important strengths. It is the first cohort study of transplant recipients to have a large enough number of incident lymphoma cases to allow assessing risks separately for a wide spectrum of subtypes. Prior efforts to quantify these risks have been limited by lack of data on lymphoma subtypes, or small size and restriction to special subgroups of transplant patients, for example, kidney recipients (Vajdic *et al*, 2010) or Medicare beneficiaries over age 65 years (Quinlan *et al*, 2010). Our cohort included a well-defined, population-based sample of the US transplant population, and linkage with corresponding population-based cancer registries allowed for highly complete, uniform cancer ascertainment.

Among the study's limitations, we note that lymphoma subtype classifications were derived from cancer registry abstractions of medical records, which may not have been standard and may have been affected by changes in lymphoma diagnostic practice over time. Our prior studies of cancer registry classification of lymphoma subtypes suggest good reliability for some subtypes (e.g., DLBCL, follicular lymphoma) (Clarke *et al*, 2004, 2006). However, misclassification would be more likely for less common

NHL subtypes and for cases diagnosed in the earlier years of this study before widespread dissemination of the international consensus guidelines (Clarke *et al*, 2004, 2006). In addition, we could not examine risks across the full spectrum of PTLDs, because US cancer registries collect information only for cases deemed malignant by a pathologist. Despite the large number of NHL cases, we did not have adequate numbers of rare subtypes, including most T-cell lymphomas, to reliably assess risk according to age or time since transplant. We note that our estimated risk for overall NHL included CLL, which is now understood to be the same entity as SLL (Turner *et al*, 2010). Inclusion of CLL/SLL decreased the SIR for overall NHL, which affects comparisons with previous reports (Kasiske *et al*, 2004; Caillard *et al*, 2006; Vajdic *et al*, 2006; Giordano *et al*, 2007; Serraino *et al*, 2007; Jiang *et al*, 2008, 2010; Baccarani *et al*, 2009; Quinlan *et al*, 2010; Engels *et al*, 2011). Finally, we lacked information on tumour EBV status, and hence we could not separately examine the risk for EBV-defined lymphoma subtypes.

In conclusion, we found substantial differences in the risk for individual lymphoma subtypes and varying patterns in association with age, transplanted organ, and time since transplantation. These results highlight that NHL should not be considered a single entity in studies of lymphoid malignancy or PTLD after transplant. There is a characteristic clinical spectrum of NHL subtypes among transplant recipients. Because lymphoma treatment varies by subtype, patients suspected of having lymphoma should receive a detailed haematopathologic workup. Our findings also provide new insight into the importance of immunosuppression for the development of some lymphoma subtypes. Future research will require large and representative case series with detailed pathologic classification to untangle the complex effects of host characteristics, oncogenic viral infections, iatrogenic immunosuppression, chronic antigen stimulation, and age-related immune senescence on development of NHL.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DISCLAIMER

The ideas and opinions expressed herein are those of the authors and endorsement by the National Cancer Institute, Health Resources and Services Administration, SRTR, the Centers for Disease Control and Prevention, and individual state cancer registries or their Contractors and Subcontractors is not intended nor should be inferred.

REFERENCES

Andreone P, Gramenzi A, Lorenzini S, Biselli M, Cursaro C, Pileri S, Bernardi M (2003) Posttransplantation lymphoproliferative disorders. *Arch Intern Med* **163**: 1997–2004.

Baccarani U, Piselli P, Serraino D, Adani GL, Lorenzin D, Gambato M, Buda A, Zanus G, Vitale A, De Paoli A, Cimaglia C, Bresadola V, Toniutto P, Risaliti A, Cillo U, Bresadola F, Burra P (2009) Comparison of de novo tumours after liver transplantation with incidence rates from Italian cancer registries. *Dig Liver Dis* **42**: 55–60.

Bierman PJ, Vose JM, Langnas AN, Rifkin RM, Hauke RJ, Smir BN, Greiner TC (1996) Hodgkin's disease following solid organ transplantation. *Ann Oncol* **7**: 265–270.

Biggar RJ, Chaturvedi AK, Goedert JJ, Engels EA (2007) AIDS-related cancer and severity of immunosuppression in persons with AIDS. *J Natl Cancer Inst* **99**: 962–972.

Busnach G, Piselli P, Arbustini E, Baccarani U, Burra P, Carrieri MP, Citterio F, De Juli E, Bellelli S, Pradier C, Rezza G, Serraino D (2006) Immunosuppression and cancer: a comparison of risks in recipients of organ transplants and in HIV-positive individuals. *Transplant Proc* **38**: 3533–3535.

Bustami RT, Ojo AO, Wolfe RA, Merion RM, Bennett WM, McDiarmid SV, Leichtman AB, Held PJ, Port FK (2004) Immunosuppression and the risk of post-transplant malignancy among cadaveric first kidney transplant recipients. *Am J Transplant* **4**: 87–93.

Caillard S, Lelong C, Pessione F, Moulin B (2006) Post-transplant lymphoproliferative disorders occurring after renal transplantation in adults: report of 230 cases from the French Registry. *Am J Transplant* **6**: 2735–2742.

Carbone A, Cesarman E, Spina M, Gloghini A, Schulz TF (2009) HIV-associated lymphomas and gamma-herpesviruses. *Blood* **113**: 1213–1224.

Clarke CA, Glaser SL, Dorfman RF, Bracci PM, Eberle E, Holly EA (2004) Expert review of non-Hodgkin's lymphomas in a population-based cancer registry: reliability of diagnosis and subtype classifications. *Cancer Epidemiol Biomarkers Prev* **13**: 138–143.

Clarke CA, Undurraga DM, Harasty PJ, Glaser SL, Morton LM, Holly EA (2006) Changes in cancer registry coding for lymphoma subtypes: reliability over time and relevance for surveillance and study. *Cancer Epidemiol Biomarkers Prev* **15**: 630–638.

de Sanjose S, Benavente Y, Vajdic CM, Engels EA, Morton LM, Bracci PM, Spinelli JJ, Zheng T, Zhang Y, Franceschi S, Talamini R, Holly EA, Grulich AE, Cerhan JR, Hartge P, Cozen W, Boffetta P, Brennan P, Maynadie M, Cocco P, Bosch R, Foretova L, Staines A, Becker N, Nieters A (2008) Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium. *Clin Gastroenterol Hepatol* **6**: 451–458.

Deepak P, Sifuentes H, Sherid M, Stobaugh D, Sadozai Y, Ehrenpreis ED (2013) T-cell non-Hodgkin's lymphomas reported to the FDA AERS with tumor necrosis factor-alpha (TNF-alpha) inhibitors: results of the REFURBISH study. *Am J Gastroenterol* **108**: 99–105.

Dharnidharka VR, Lamb KE, Gregg JA, Meier-Kriesche HU (2012) Associations between EBV serostatus and organ transplant type in PTLD risk: an analysis of the SRTR National Registry Data in the United States. *Am J Transplant* **12**: 976–983.

Engels EA (2007) Infectious agents as causes of non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev* **16**: 401–404.

Engels EA, Biggar RJ, Hall HI, Cross H, Crutchfield A, Finch JL, Grigg R, Hylton T, Pawlish KS, McNeel TS, Goedert JJ (2008) Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer* **123**: 187–194.

Engels EA, Pfeiffer RM, Fraumeni Jr. JF, Kasiske BL, Israni AK, Snyder JJ, Wolfe RA, Goodrich NP, Bayakly AR, Clarke CA, Copeland G, Finch JL, Fleissner ML, Goodman MT, Kahn A, Koch L, Lynch CF, Madeleine MM, Pawlish K, Rao C, Williams MA, Castenson D, Curry M, Parsons R, Fant G, Lin M (2011) Spectrum of cancer risk among US solid organ transplant recipients. *JAMA* **306**: 1891–1901.

Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM, Biggar RJ (2006) Trends in cancer risk among people with AIDS in the United States 1980-2002. *AIDS* **20**: 1645–1654.

Giordano TP, Henderson L, Landgren O, Chiao EY, Kramer JR, El-Serag H, Engels EA (2007) Risk of non-Hodgkin lymphoma and lymphoproliferative precursor diseases in US veterans with hepatitis C virus. *JAMA* **297**: 2010–2017.

Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM (2007) Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* **370**: 59–67.

Hellgren K, Iliadou A, Rosenquist R, Feltelius N, Backlin C, Enblad G, Askling J, Baecklund E (2010) Rheumatoid arthritis, treatment with corticosteroids and risk of malignant lymphomas: results from a case-control study. *Ann Rheum Dis* **69**: 654–659.

Jagadeesh D, Woda BA, Draper J, Evens AM (2012) Post transplant lymphoproliferative disorders: risk, classification, and therapeutic recommendations. *Curr Treat Options Oncol* **13**: 122–136.

Jenson HB (2011) Epstein-Barr virus. *Pediatr Rev* **32**: 375–383, quiz 384.

Jiang Y, Villeneuve PJ, Fenton SS, Schaubel DE, Lilly L, Mao Y (2008) Liver transplantation and subsequent risk of cancer: findings from a Canadian cohort study. *Liver Transpl* **14**: 1588–1597.

Jiang Y, Villeneuve PJ, Wielgosz A, Schaubel DE, Fenton SS, Mao Y (2010) The incidence of cancer in a population-based cohort of Canadian heart transplant recipients. *Am J Transplant* **10**: 637–645.

Kasiske BL, Snyder JJ, Gilbertson DT, Wang C (2004) Cancer after kidney transplantation in the United States. *Am J Transplant* **4**: 905–913.

Knight JS, Tsodikov A, Cibrik DM, Ross CW, Kaminski MS, Blayney DW (2009) Lymphoma after solid organ transplantation: risk, response to therapy, and survival at a transplantation center. *J Clin Oncol* **27**: 3354–3362.

LaCasce AS (2006) Post-transplant lymphoproliferative disorders. *Oncologist* **11**: 674–680.

Mason M, Siegel CA (2013) Do inflammatory bowel disease therapies cause cancer? *Inflamm Bowel Dis* **19**(6): 1306–1321.

Mbulaiteye SM, Biggar RJ, Goedert JJ, Engels EA (2003) Immune deficiency and risk for malignancy among persons with AIDS. *J Acquir Immune Defic Syndr* **32**: 527–533.

Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS (2006) Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. *Blood* **107**: 265–276.

Opelz G, Daniel V, Naujokat C, Dohler B (2009) Epidemiology of pretransplant EBV and CMV serostatus in relation to posttransplant non-Hodgkin lymphoma. *Transplantation* **88**: 962–967.

Opelz G, Dohler B (2004) Lymphomas after solid organ transplantation: a collaborative transplant study report. *Am J Transplant* **4**: 222–230.

Quinlan SC, Landgren O, Morton LM, Engels EA (2010) Hodgkin lymphoma among US solid organ transplant recipients. *Transplantation* **90**: 1011–1015.

Quinlan SC, Morton LM, Pfeiffer RM, Anderson LA, Landgren O, Warren JL, Engels EA (2010) Increased risk for lymphoid and myeloid neoplasms in elderly solid-organ transplant recipients. *Cancer Epidemiol Biomarkers Prev* **19**: 1229–1237.

Quinlan SC, Pfeiffer RM, Morton LM, Engels EA (2011) Risk factors for early-onset and late-onset post-transplant lymphoproliferative disorder in kidney recipients in the United States. *Am J Hematol* **86**: 206–209.

Serraino D, Piselli P, Busnach G, Burra P, Citterio F, Arbustini E, Baccarani U, De Juli E, Pozzetto U, Bellelli S, Polesel J, Pradier C, Dal Maso L, Angeletti C, Carrieri MP, Rezza G, Franceschi S (2007) Risk of cancer following immunosuppression in organ transplant recipients and in HIV-positive individuals in southern Europe. *Eur J Cancer* **43**: 2117–2123.

Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (eds (2008) *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. France International Agency for Research on Cancer: Lyon.

Tsao L, Hsi ED (2007) The clinicopathologic spectrum of posttransplantation lymphoproliferative disorders. *Arch Pathol Lab Med* **131**: 1209–1218.

Turner JJ, Morton LM, Linet MS, Clarke CA, Kadin ME, Vajdic CM, Monnereau A, Maynadie M, Chiu BC, Marcos-Gragera R, Costantini AS, Cerhan JR, Weisenburger DD (2010) InterLymph hierarchical classification of lymphoid neoplasms for epidemiologic research based on the WHO Classification (2008): update and future directions. *Blood* **116**(20): e90–e98.

Vajdic CM, McDonald SP, McCredie MR, van Leeuwen MT, Stewart JH, Law M, Chapman JR, Webster AC, Kaldor JM, Grulich AE (2006) Cancer incidence before and after kidney transplantation. *JAMA* **296**: 2823–2831.

Vajdic CM, van Leeuwen MT (2009) Cancer incidence and risk factors after solid organ transplantation. *Int J Cancer* **125**: 1747–1754.

Vajdic CM, van Leeuwen MT, Turner JJ, McDonald AM, Webster AC, McDonald SP, Chapman JR, Kaldor JM, Grulich AE (2010) No excess risk of follicular lymphoma in kidney transplant and HIV-related immunodeficiency. *Int J Cancer* **127**: 2732–2735.

van Leeuwen MT, Grulich AE, Webster AC, McCredie MR, Stewart JH, McDonald SP, Amin J, Kaldor JM, Chapman JR, Vajdic CM (2009) Immunosuppression and other risk factors for early and late non-Hodgkin lymphoma after kidney transplantation. *Blood* **114**: 630–637.

van Leeuwen MT, Vajdic CM, Middleton MG, McDonald AM, Law M, Kaldor JM, Grulich AE (2009) Continuing declines in some but not all HIV-associated cancers in Australia after widespread use of antiretroviral therapy. *AIDS* **23**: 2183–2190.