

Title: No excess risk of follicular lymphoma in kidney transplant and HIV-related immune deficiency

Short title: Follicular lymphoma in immune deficiency

Authors: Claire M. Vajdic¹, Marina T. van Leeuwen^{2,3}, Jennifer J. Turner⁴, Ann M. McDonald², Angela C. Webster^{5,6,7}, Stephen P. McDonald^{5,8}, Jeremy R. Chapman⁷, John M. Kaldor², Andrew E. Grulich²

Affiliations of authors:

¹UNSW Cancer Research Centre, Prince of Wales Clinical School, University of New South Wales, Sydney, Australia;

²National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia;

³School of Public Health and Community Medicine, University of New South Wales, Sydney, Australia;

⁴Department of Anatomical Pathology, St Vincent's Hospital, Sydney, Australia;

⁵Australia and New Zealand Dialysis and Transplant Registry, Queen Elizabeth Hospital, Adelaide, Australia;

⁶School of Public Health, University of Sydney, Sydney, Australia;

⁷Centre for Transplant and Renal Research, Millennium Institute, Westmead Hospital, University of Sydney, Sydney, Australia;

⁸Disciplines of Medicine and Public Health, University of Adelaide, Adelaide, Australia

Corresponding author: Claire M. Vajdic PhD, Senior Research Fellow, Lowy Cancer Research Centre, Prince of Wales Clinical School, Faculty of Medicine, University of NSW,

Sydney NSW 2052, Australia. Tel: (612) 9385 1424. Fax: (612) 9385 1430. Email:

claire.vajdic@unsw.edu.au

Short report

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Abstract

Subtype-specific incidence patterns in populations at high-risk of lymphoma offer insight into lymphomagenesis. The incidence profiles for the two most common non-Hodgkin lymphoma subtypes were compared for two immune-deficient populations, adults receiving a kidney transplant 1982-2003 (n=7,730) or diagnosed with HIV infection 1982-2004 (n=17,175). National population-based registries were linked and standardized incidence ratios (SIRs) were computed for each cohort and lymphoma subtype. Risk of diffuse large B-cell lymphoma was significantly increased after transplantation (SIR 17.83, 95%CI 13.61-22.95) and after HIV infection (SIR 58.81, 95%CI 52.59-65.56). Rates of follicular lymphoma were neither significantly increased nor decreased in transplant recipients (SIR 0.82, 95%CI 0.10-2.96) and in people with HIV (SIR 1.25, 95%CI 0.41-2.91). The findings argue against an infectious or other immune-deficiency-related aetiology for follicular lymphoma, and clearly differentiate it from diffuse large B-cell lymphoma.

Key words: non-Hodgkin lymphoma, incidence, HIV, transplantation, immune deficiency

Non-Hodgkin lymphoma (NHL) is an immune-deficiency associated malignancy, occurring at markedly increased rates in people with HIV-related, iatrogenic, and congenital immune deficiency.¹⁻³ NHL includes an array of lymphoma subtypes displaying morphological, clinical, and prognostic heterogeneity.⁴ Despite this heterogeneity, consistent evidence of variation in etiological associations for the most common variants is limited, although it has been hypothesized that immune dysfunction may be more important for diffuse large B-cell NHL (DLBCL) than for follicular lymphoma (FL).⁵ A comparison of the lymphoma subtype-specific incidence profiles for immunodeficient populations may support different mechanisms for lymphomagenesis by subtype.

Here we report population-based standardized incidence ratios (SIRs) for the two most common World Health Organization (WHO) 2001 NHL subtypes in national cohorts of adult kidney transplant recipients and adults with HIV infection.

Material and methods

The transplant cohort included all adults (16-80 years) receiving a kidney transplant in Australia 1982-2003 (n=7,730), as notified to the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). The ANZDATA Registry is a population-based register of all patients who commenced chronic dialysis or receive a kidney transplant in Australia and New Zealand, collected via surveys of patients' treating dialysis or transplant units.

The HIV cohort included all adults (16-80 years) diagnosed with HIV in Australia from 1982 until 2004 (n=20,232), as notified to the Australian National HIV/AIDS Registries. HIV infection and AIDS are separately notifiable conditions in Australia⁶, and nationwide HIV surveillance commenced in 1989⁷. As NHL is an AIDS-defining cancer, analysis of NHL incidence was restricted to people with a known date of HIV diagnosis (n=17,175, 85%); people notified only with AIDS were excluded.

Incident lymphomas were ascertained using probabilistic data linkage between each cohort and the Australian National Cancer Statistics Clearing House (NCSCH).^{8,9} This database records incident invasive cancers diagnosed in Australian residents since 1st January 1982, except non-melanoma skin cancer, as notified by statute to the jurisdictional cancer registries. For each matched record, the date of diagnosis and the tumor topography (ICD-10) and morphology (ICD-O-3) codes were obtained. The classification of DLBCL and FL was stable over the entire period of follow-up¹⁰, and the lymphoma subtypes were classified according to current guidelines for epidemiological research⁴.

Person-years (PY) of follow-up commenced on the date of HIV diagnosis or the date of kidney transplantation. PY were accrued until the date of lymphoma diagnosis, 80 years of age, death, or the last date of cancer registration, whichever occurred first. For kidney transplant recipients, PY were accrued only during periods of transplant function; time on dialysis after graft failure and before re-transplantation did not contribute.

SIR with 95% exact CI were computed assuming a Poisson distribution¹¹ and compared the number of observed cases in each cohort with that expected based on the application of five-year age-, sex-, state/territory-, and calendar-year-specific general population subtype-specific incidence rates.

All analyses were performed using Stata version 10 (StataCorp LP, College Station, Tex).

Approval for the use of the datasets for the purpose of data linkage was obtained from all relevant data custodians and institutional review boards. The need for informed consent was waived on account of the researchers receiving only de-identified data.

Results

In total, there were 50,472 PY (mean 6.5) of follow-up after transplantation and 135,179 PY (mean 7.9) of follow-up after HIV diagnosis (Table 1). Compared to transplant

recipients, people with HIV infection were far more likely to be male ($p < 0.0001$) and substantially younger ($p < 0.0001$). These differences precluded a quantitative comparison of the subtype-specific SIRs. A total of 117 NHLs were observed in transplant recipients and 661 in people with HIV. In both cohorts, the risk of DLBCL was significantly raised, and there was no significant increase or decrease in risk of FL (Table 2). As a large proportion (35-40%) of incident NHLs was unclassifiable in each cohort, a sensitivity analysis was performed and a proportionate number of NOS NHLs were counted as FL. These sensitivity analyses did not alter the incidence estimates for FL (SIR 1.23 (95% CI 0.25-3.59) in kidney transplant recipients, SIR 2.00 (95% CI 0.86-3.93) in people with HIV).

Discussion

This national, population-based study examined the risk of DLBL and FL in two immune-deficient populations using identical methods, over the same time period. We found that DLBCL incidence was significantly increased in both populations. The novel finding regarding the implications for lymphomagenesis was that in both cohorts, FL risk did not differ from that of the background population in either cohort. In both, immunodeficiency is characterized by a reduction, or depletion in function of T helper cells^{13, 14} and both are known to be at excess risk of neoplasms with an infectious cause¹². These observations argue against a predominant role for a known, or as yet unidentified, oncogenic infectious agent, in FL pathogenesis. Furthermore, as immunodeficiency in both populations is characterized by a reduction, or depletion in function of T helper cells^{13, 14}, this finding suggests that the malignant transformation and expansion of germinal-centre derived follicular B-cells is not under the direct control of cellular immunity.

Excess risk of DLBCL in people with HIV infection is well-established¹⁵ and NHL risk is strongly correlated with the current severity of HIV-related immunodeficiency¹⁶. Previous SIR data on the risk of DLBCL after transplantation is limited to a non-population-

based cohort study of 78 histopathologically verified incident cases (1964-2007) which found a significant excess risk (SIR 32).¹⁷ Much of the excess risk of DLBCL in immunodeficiency can be attributed to the inability to mount an effective immune response against Epstein-Barr virus (EBV) infection or reactivation.^{18, 19} EBV is present in up to 80% of DLBCL in people with HIV² and is also present in a sizable proportion of post-transplant lymphoproliferative disorders², particularly those occurring early after transplantation²⁰.

Unlike DLBCL, follicular lymphoma is not a specified AIDS-defining condition, and involvement of EBV, or another infections oncologic agent has not been established. The risk of FL in people with HIV infection relative to the general population has been quantified in only one prior population-based study (1975-1990), for a cohort defined by a non-NHL related AIDS diagnosis (SIR 6.83, 95% CI 1.86-17.48).²¹ For transplantation, risk relative to the general population has been quantified in one non-population-based study (0 observed and 0.4 expected cases; $p=0.98$).¹⁷ There are no published subtype-specific SIR estimates for NHL in other forms of immune dysregulation, including primary immune deficiency and autoimmune disease. However, other epidemiological evidence consistently shows stronger associations between autoimmune disease and DLBCL risk compared to FL risk.^{22, 23}

The key strength of this study is its population-base, including the cancer ascertainment, which minimized bias by using the same approach for the cohorts and the general population, and high quality cancer registration processes (Curado2007; Tracey2009). Accordingly however, histopathological review was not possible. A large proportion (35-40%) of incident NHLs were unclassifiable, demonstrating the difficulty of accurate lymphoma diagnosis in these immunosuppressed hosts; however, the reliability of FL diagnosis is at least 89%.^{4, 10} Despite this uncertainty, sensitivity analyses did not alter the significance of the SIR estimate for FL for either cohort. In addition, while we restricted the

study to adults, the elderly are largely unrepresented in these cohorts, and thus the expected numbers of lymphomas were low.

Using a large-scale, systematic approach, we quantified the site-specific NHL risk in two immune deficient states and found no association with FL. We believe this indicates that FL occurring in the context of HIV-related and iatrogenic immunosuppression is unlikely to be related to the patient's immune function. This data adds to the evidence that FL is etiologically distinct from the most common NHL subtype, DLBCL.

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Authorship

Contribution: C.M.V., M.T.v.L., J.J.T., A.M.M., A.C.W., S.P.M., J.R.C, J.M.K. and A.E.G. designed the research, interpreted data, and revised and reviewed the final manuscript; M.T.v.L. performed statistical analysis; and C.M.V., M.T.v.L, J.J.T and A.E.G were responsible for drafting the manuscript.

Conflict of interest disclosure

The authors report no potential conflicts of interest.

Table 1. Characteristics of the adult Australian immune deficiency cohorts.

Characteristic	Kidney transplant cohort		HIV cohort	
	n (%)	PY (mean)	n (%)	PY (mean)
Total	7 730 (100)	50 472 (6.5)	17 175 (100)	135 179 (7.9)
Sex				
Male	4 573 (59)	29 747 (6.5)	15 755 (92)	125 372 (8.0)
Female	3 157 (41)	20 725 (6.6)	1 420 (8)	9 806 (6.9)
Age at start of follow-up ¹				
16-30	1 442 (19)	11 009 (7.6)	6 100 (36)	57 822 (9.5)
30-39	1 560 (20)	11 020 (7.1)	6 421 (37)	49 047 (7.6)
40-49	1 909 (25)	12 767 (6.7)	3 044 (18)	19 938 (6.7)
50-59	1 928 (25)	11 420 (5.9)	1 165 (7)	6 514 (5.6)
60-69	859 (11)	4 172 (4.9)	377 (2)	1 684 (4.5)
70-80	32 (0.4)	84 (2.6)	68 (0.4)	173 (2.5)
Calendar period ²				
1982/85-1995	4 736 (61)	22 286 (4.7)	10 181 (59)	48 271 (4.7)
1996-1999	4 920 (64)	14 698 (3.0)	10 281 (60)	33 031 (3.2)
2000-2003/04/05	5 600 (72)	13 488 (2.4)	13 277 (77)	53 877 (4.1)

¹Follow-up commences at HIV diagnosis or first transplant

²Calendar period time dependent

Table 2. Standardized incidence ratios for NHL overall and the major NHL subtypes in the adult Australian immune deficiency cohorts.

NHL type ¹	Kidney transplant cohort ² 1982-2003			HIV cohort 1982-2004		
	Obs (Exp)	SIR	95% CI	Obs (Exp)	SIR	95% CI
All NHL	117 (12.78)	9.16	7.57-10.97	661 (19.07)	34.67	32.08-37.42
All B-cell	72 (10.29)	6.99	5.47-8.81	383 (14.97)	25.59	23.09-28.28
DLBCL	60 (3.36)	17.83	13.61-22.95	325 (5.53)	58.81	52.59-65.56
Follicular lymphoma	2 (2.44)	0.82	0.10-2.96	5 (4.01)	1.25	0.41-2.91
NHL NOS	41 (1.88)	21.79	15.64-29.56	266 (3.01)	88.46	78.15-99.76

Obs observed

Exp expected

SIR standardized incidence ratio

CI confidence interval

NHL Non-Hodgkin lymphoma

DLBCL Diffuse large B-cell lymphoma

NOS Not otherwise specified.

¹ICD10/O-3 codes: NHL 9591, 9670-9729, 9820-9837, 9940, 9948 and 9590 if ICD10 C82-C85; B-cell NHL 9670-9699, 9728, 9823, 9826, 9833, 9836, 9940; DLBL 9680, 9684, 9678, 9679; Follicular 9690, 9691, 9695, 9698; NOS 9591, 9727, 9820, 9832, 9835, 9590 (if site C82-C85)

²Only NHLs diagnosed during transplant function, either first or higher-order grafts, were counted

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