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Risk of non-Hodgkin lymphoma subtypes in HIV-infected people during the HAART era: a population-based study

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Abstract

Objective—HIV-infected people have greatly elevated risk of non-Hodgkin lymphoma (NHL), particularly the AIDS-defining NHL subtypes: diffuse large B-cell lymphoma, Burkitt lymphoma and primary lymphomas arising in the central nervous system. The goals of this analysis were to comprehensively describe risks of NHL subtypes, especially those not well studied, among HIV/AIDS patients; examine risks specifically in the HAART era; and distinguish risks in HIV-infected individuals prior to diagnosis with AIDS.

Design—Population-based registry linkage study.

Methods—We used data from the US HIV/AIDS Cancer Match Study from 1996 to 2010 (*N* = 273 705) to calculate standardized incidence ratios (SIRs) comparing subtype specific NHL risks in HIV-infected people to those in the general population, and used Poisson regression to test for differences in SIRs between the HIV-only and AIDS periods.

Results—NHL risk was elevated 11-fold compared to the general population, but varied substantially by subtype. AIDS-defining NHL subtypes comprised the majority, and risks were high (SIRs ≥ 17), but risks were also increased for some T-cell lymphomas (SIRs = 3.6–14.2), marginal zone lymphoma (SIR = 2.4), lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (SIR = 3.6), and acute lymphoblastic leuke mia/lymphoma (SIR = 2.4).

Conclusion—HIV-infected people in the HAART era continue to have elevated risk of AIDS-defining NHL subtypes, highlighting the contribution of moderate and severe immunosuppression to their cause. Whereas non-AIDS-defining subtypes are much less common, immunosuppression

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Conflicts of interest

The authors have no conflicts of interest to disclose.

or other dysregulated immune states likely play a role in the cause of some T-cell lymphomas, marginal zone lymphoma, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, and acute lymphoblastic leukemia/lym phoma.

Keywords

AIDS; AIDS-related; epidemiology; HIV; lymphoma; non-Hodgkin lymphoma

Introduction

HIV infection causes progressive immune impairment, potentially leading to AIDS. HIV-infected people have greatly elevated risk of non-Hodgkin lymphoma (NHL), particularly subtypes classified as 'AIDS-defining events' [1]: diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, and primary lymphomas of the central nervous system (CNS) [2,3]. However, HIV-associated risk for other NHL subtypes remains poorly understood.

Among HIV-infected people, widespread adoption of HAART beginning in 1996 has improved HIV-related immunodeficiency and decreased overall NHL incidence [4,5]. Characterizing risk of specific AIDS-defining and non-AIDS-defining NHL subtypes in the HAART era can provide insights into the causative role of immunodeficiency across the spectrum of NHL subtypes.

Methods

We examined risk of NHL subtypes in HIV-infected people using population-based data from the HIV/AIDS Cancer Match (HACM) Study [3]. Briefly, HIV/AIDS and cancer registry data were linked in seven US states with name-based registration of HIV infection: Colorado (systematic registration starting in 1991), Connecticut (2002), Florida (1998), Georgia (2004), Michigan (1992), New Jersey (1992), and Texas (1997). Our analysis included 273 705 people registered with HIV infection without AIDS (i.e. HIV-only) or with AIDS and followed during 1996–2010 (N = 1 459 816 person-years). Incident NHL cases were identified from cancer registries, and NHL subtypes were classified using International Classification of Disease for Oncology (3rd edition, ICD-O3) topography and morphology codes (Supplemental Table 1, http://links.lww.com/QAD/A566). We also separately examined risk of primary CNS lymphoma regardless of histologic subtype. The HACM Study was approved by human patient committees at participating registries as required.

For the primary analysis, follow-up started at the later of HIV report (AIDS diagnosis if HIV was not reported earlier) or start of systematic HIV reporting to the registry. Follow-up ended at the earliest of NHL diagnosis, death, or end of cancer registry coverage. We conducted further analyses separately during the HIV-only versus AIDS intervals (representing lesser or greater degrees of immunosuppression, respectively). For AIDS-defining NHL subtypes, the HIV-only analysis examined risk of NHL as an AIDS-defining event in those reported with HIV, whereas the AIDS analysis examined risk among people already diagnosed with AIDS based on another indication. Notably, incidence for the AIDS-defining NHL subtypes was very high in the first 3 months after AIDS diagnosis, likely reflecting slight differences in diagnosis dates reported to the HIVand cancer registries.

Thus, we included the first 3 months after AIDS diagnosis in the HIV-only period. However, the comparisons of NHL subtype risks for the HIV-only versus AIDS intervals described below remained similar if cases in the first 3 months were instead counted in the AIDS period (data not shown). Because we did not have information on the at-risk HIV group until they were reported to the HIV registry, we did not include NHL cases where HIV report, AIDS diagnosis and NHL diagnosis occurred simultaneously (or NHL was diagnosed within 3 months of both HIV and AIDS for AIDS-defining subtypes).

In each analysis, we compared risk in HIV-infected people to the general population using standardized incidence ratios (SIRs = observed cases/expected cases). Expected cases were derived by applying general population cancer rates from the registries to person-time at risk in the HIV-infected cohort, stratified by sex, age, race/ethnicity, calendar year, and registry. We used Poisson regression to test for differences in SIRs between the HIV-only and AIDS periods, and across calendar periods.

Results

Ninety percent of the 2828 cases of NHL diagnosed in the HIV-infected people were one of the AIDS-defining histologic subtypes [50% DLBCL, 9% Burkitt lymphoma, and 31% NHL-not otherwise specified (NOS); Table 1]. We included NHL-NOS as an AIDS-defining subtype for presentation of results, because these likely comprised mostly DLBCL, and SIRs were similar for these two subtypes. Almost all CNS lymphomas were DLBCL (40%) or NHL-NOS (57%), but if other histologic subtypes arising in the CNS were included ($N = 14$), then 91% of NHLs were AIDS-defining subtypes (Table 1).

Risks were elevated 11-fold for NHL overall and at least 17-fold compared to the general population for all AIDS-defining subtypes (Table 1), with the greatest elevations observed for Burkitt lymphoma (SIR = 33.7) and CNS lymphoma (SIR = 47.7). Risks were significantly greater in the AIDS period compared to the HIV-only period for DLBCL, NHL-NOS and CNS lymphoma ($P < 0.0001$; Table 2). Notably, Burkitt lymphoma risk did not differ between the HIV-only and AIDS periods. SIRs were significantly lower during 2003–2010 than 1996–2002 for DLBCL, CNS lymphomas and NHL-NOS, but not for Burkitt lymphoma (Supplemental Table 2, http://links.lww.com/QAD/A566).

All non-AIDS-defining subtypes combined comprised the remaining 10% of NHL cases. The most common subtypes were anaplastic large cell lymphoma (ALCL, $N = 68$), peripheral T-cell lymphoma (PTCL, $N = 39$), and follicular lymphoma ($N = 44$).

Among the non-AIDS-defining subtypes, risks relative to the general population were elevated for ALCL (SIR = 14.2), natural killer (NK)/T-cell lymphoma (SIR = 3.9), PTCL (SIR = 3.6), lymphoplasmacytic lymphoma (LPL)/Waldenström macroglobulinemia (SIR = 3.6), marginal zone lymphoma (SIR = 2.4), and acute lymphoblastic leukemia/lymphoma (ALL; SIR = 2.4; Table 1). In contrast, risk was not significantly different from the general population for follicular lymphoma, chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), mantle cell lymphoma, mycosis fungoides/Sézary syndrome, or other rarer NHL subtypes. Risks of ALCL and PTCL were significantly greater in the

AIDS period compared to the HIV-only period (P = 0.0003 and 0.03, respectively), whereas there was no difference by AIDS status for NK/T-cell lymphoma, LPL/Waldenström macroglobulinemia, marginal zone lymphoma, or ALL (Table 2). SIRs were lower for all non-AIDS-defining subtypes during 2003–2010 than 1996–2002, though the differences by time period were statistically significant only for ALCL and CLL/SLL (Supplemental Table 2, http://links.lww.com/QAD/A566).

Discussion

Non-Hodgkin lymphoma risk in HIV-infected people in developed countries has diminished with widespread use and effectiveness of HAART [4,5]. Nonetheless, our results demonstrate that risk remains greatly elevated relative to the general population, even among the growing fraction of the population infected with HIV, but not diagnosed with AIDS. While NHL has often been considered as a single cancer entity for studies of HIV-infected people, we provide the first comprehensive evidence of substantial heterogeneity in HIV-related risks for distinct NHL subtypes.

The considerable elevation in risk for AIDS-defining NHL subtypes in the HAART era is consistent with previous studies [3,5] and the increased risk in those with AIDS compared to those with HIV-only supports severity of immune deficiency as a primary determinant of risk for these subtypes. Among HIV-infected people, loss of immune control of Epstein–Barr virus (EBV) is key to the cause of CNS lymphoma and DLBCL [6]. For DLBCL and CNS lymphomas, the magnitude of risk and the differences between the HIV-only and AIDS intervals that we observed were somewhat smaller than reported previously [3,5], possibly due to our inclusion of more recent follow-up time with improved HIV therapy. Indeed, risk of these subtypes decreased over time in our study, likely reflecting improved uptake and effectiveness of antiretroviral therapy [7]. Results for NHL-NOS were similar to those for DLBCL, suggesting the NHL-NOS category was comprised largely of unclassified DLBCL or cases of plasmablastic morphology that did not have specific ICD-O3 codes prior to 2008. Burkitt lymphoma risk was similar in people with HIV-only and AIDS and did not decrease over time, perhaps reflecting a somewhat complex relationship with degree of immunosuppression [8].

Although the AIDS-defining subtypes still comprise the vast majority of NHL cases, it is increasingly important to understand the risks of non-AIDS-defining cancers as people live longer with HIV. We found significantly elevated risk for several T-cell lymphoma subtypes (ALCL, PTCL, NK/T cell), extending previous findings among people with AIDS from the pre-HAARTera [9]. ALCL and PTCL risks were significantly higher in people with AIDS than with HIV-only, and ALCL risk declined over time, pointing to the importance of immunodeficiency in the cause of these subtypes.

The elevated risks we found for marginal zone lymphoma, LPL/Waldenström macroglobulinemia, and ALL support a role for HIV in the cause of these subtypes, but similar risks in people with HIV-only and AIDS suggest mechanisms other than immune deficiency. Chronic antigenic stimulation by persistent infection [e.g. with *Helicobacter pylori*, hepatitis C virus (HCV)], autoimmune disease, or blood transfusion has been

implicated in the cause of both marginal zone lymphoma and LPL/Waldenström macroglobulinemia [10–13]. Thus, the immune activation and inflammation associated with HIV infection may underlie the increased risks of these subtypes. An elevated prevalence of HCV infection among individuals with HIV may contribute to the elevated risk observed for marginal zone lymphoma, but evidence from prior studies indicates HCV may not be a risk factor for this NHL subtype in the context of immunosuppression [14–16]. We did not see an elevated risk for follicular lymphoma or CLL/SLL, in line with the previous results [17], suggesting that immune perturbation does not play a major role in development of these types of NHLs. The similarity of the NHL risk patterns in our results to those after solid organ transplantation [18] further argues for a key role for immunosuppression and other immune abnormalities in the cause of specific subtypes [19].

The primary strength of this analysis was the use of a large population-based HIV cohort with systematic ascertainment of NHL and characterization of subtypes by cancer registries. Our study extends previous findings by including more recent follow-up and by examining risks of specific non-AIDS-defining NHL subtypes. Several limitations should also be noted. We could not evaluate HAART use and $CD4^+$ cell counts in relation to risk, as these data were inconsistently available. SIRs for the AIDS-defining NHL subtypes likely underestimate the relative risk because a substantial fraction of the cases in the general population may be attributable to HIV infection (e.g. 27% of Burkitt lymphoma and 8% of DLBCL) [20,21]. Additionally, numbers were limited for assessing the risks of rare NHL subtypes. Misclassification of NHL subtypes was possible (e.g. primary effusion lymphoma expressing aberrant T-cell antigens), and 90% of NHL cases in our analysis were diagnosed prior to 2008, so the results do not reflect the most recent changes in subtype classification. Finally, approximately 16% of people with HIV in the United States have undiagnosed infection [22], but we were only able to examine NHL risk in those with diagnosed HIV infection.

In conclusion, HIV-infected people in the HAART era continue to have elevated risk of NHL, and this risk varies substantially by subtype. Most NHLs are the AIDS-defining NHL subtypes, highlighting the strong contribution of immunosuppression and EBV to their cause. Although non-AIDS-defining subtypes are much less common, immunosuppression or other dysregulated immune states likely play a role for some T-cell lymphomas, marginal zone lymphoma, LPL/Walden-ström macroglobulinemia, and ALL. Additional research should address the detailed immune mechanisms underlying these observations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Risk of non-Hodgkin lymphoma subtypes among people registered with HIV infection or AIDS in the United States (1996–2010).

NHL subtypes	Cases (*N*)	(%)	Incidence rate[a]	SIR	95% CI
AIDS-defining					
DLBCL	1404	49.6	96.2	17.6	16.7–18.6
Burkitt	262	9.3	17.9	33.7	29.7–38.0
Central nervous system	464	16.4	31.8	47.7	43.4–52.2
NHL-NOS	884	31.3	60.6	19.9	18.6–21.2
Non-AIDS-defining					
Follicular	44	1.6	3.0	1.3	1.0–1.8
CLL/SLL	30	1.1	2.1	0.8	0.5–1.2
Marginal zone	31	1.1	2.1	2.4	1.6–3.4
Mantle cell	6	0.2	0.4	1.0	0.4–2.3
LPL/WM	14	0.5	1.0	3.6	2.0–6.0
ALCL	68	2.4	4.7	14.2	11.0–18.0
Primary cutaneous ALCL	3	0.1	0.2	3.9	0.8–11.3
Peripheral T cell	39	1.4	2.7	3.6	2.6–4.9
MF/SS	5	0.2	0.3	0.8	0.3–1.8
Natural killer/T cell	4	0.1	0.3	3.9	1.1–9.9
ALL[b]	27	1.0	1.8	2.4	1.6–3.4
Other specified	7	0.2	0.5	1.1	0.4–2.2
Overall NHL[c]	2828	100	193.7	10.6	10.2–11.0

95% CI, 95% confidence interval; ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia/lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; LPL/WM, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; MF/SS, mycosis fungoides/Sézary syndrome; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; SIR, standardized incidence ratio.

[a] Cases per 100000 person-years.

[b] Includes all precursor lymphoid neoplasms.

[c] The number of overall NHL cases is the sum of the subtypes listed excluding central nervous system lymphomas, which are included in the appropriate histologic subtype categories.

Table 2

Comparison of non-Hodgkin lymphoma risk during the HIV-only and AIDS periods.

NHL subtypes	HIV-only[a]			AIDS			$P_{difference}$[b]
	Cases	SIR	95% CI	Cases	SIR	95% CI	
AIDS-defining							
DLBCL	330	11.6	10.4–12.9	1074	20.9	19.7–22.2	<0.0001
Burkitt	114	38.8	32.0–46.6	148	30.6	25.8–35.9	0.06
Central nervous system	81	22.2	17.6–27.6	383	63.0	56.8–69.6	<0.0001
NHL-NOS	203	13.1	11.3–15.0	681	23.5	21.7–25.3	<0.0001
Non-AIDS-defining							
Follicular	13	1.1	0.6–1.9	31	1.4	1.0–2.0	0.52
CLL/SLL	11	0.9	0.5–1.6	19	0.8	0.5–1.2	0.63
Marginal zone	16	3.5	2.0–5.7	15	1.8	1.0–3.0	0.06
Mantle cell	0	0	0–2.0	6	1.6	0.6–3.4	–
LPL/WM	4	3.1	0.8–7.8	10	3.9	1.8–7.1	0.70
ALCL	10	5.7	2.7–10.4	58	19.2	14.6–24.9	0.0003
Peripheral T cell	7	1.8	0.7–3.8	32	4.6	3.1–6.4	0.03
MF/SS	2	0.8	0.1–3.1	3	0.7	0.2–2.2	0.89
Natural killer/T cell	1	2.7	0.1–15.3	3	4.5	0.9–13.1	0.67
ALL[c]	12	2.7	1.4–4.7	15	2.2	1.2–3.6	0.59
Other specified	2	0.9	0.1–3.2	5	1.2	0.4–2.8	0.71
Overall NHL[d]	725	7.7	7.2–8.3	2103	12.1	11.6–12.7	<0.0001

95% CI, 95% confidence interval; ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia/lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; LPL/WM, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; MF/SS, mycosis fungoides/Sézary syndrome; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; SIR, standardized incidence ratio. Note: HIV-Only = 583692 person-years; AIDS = 876124 person-years.

[a] HIV-only period includes the first three months after AIDS diagnosis in those who also developed AIDS; for AIDS-defining subtypes, cases in the HIV-only period are comprised of NHLs that occurred as the AIDS-defining event.

[b] Test for difference of SIRs in the HIV-only and AIDS periods, using Poisson regression models with sex and age.

[c] Includes all precursor lymphoid neoplasms.

[d] The number of overall NHL cases is the sum of the subtypes listed, excluding central nervous system lymphomas, which are included in the appropriate histologic subtype categories.