HHS Public Access

Author manuscript

*AIDS*. Author manuscript; available in PMC 2021 July 01.

Published in final edited form as:

*AIDS*. 2020 July 01; 34(8): 1237–1245. doi:10.1097/QAD.0000000000002528.

# Cancer risk following lymphoid malignancies among HIV-infected people

**Parag Mahale**[a], **Chinenye Ugoji**[b], **Eric A. Engels**[a], **Meredith S. Shiels**[a], **Sally Peprah**[a], **Lindsay M. Morton**[c]

[a]Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, Department of Health and Human Services, National Cancer Institute, National Institutes of Health, Bethesda,

[b]Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore,

[c]Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, Department of Health and Human Services, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA.

## Abstract

**Objective(s):** HIV-infected people have increased cancer risk. Lymphoma survivors have an increased risk of certain second primary cancers in the general population, but second cancer risk among HIV-infected people is poorly understood. Herein, we characterized the risk of cancers following lymphoid malignancies among HIV-infected people.

**Design:** Population-based linkage of HIV and cancer registries.

**Methods:** We used data from the US HIV/AIDS Cancer Match Study (1996–2015) and evaluated the risk of first nonlymphoid malignancy in Cox regression models, with first lymphoid malignancy diagnosis as a time-dependent variable.

**Results:** Among 531 460 HIV-infected people included in our study, 6513 first lymphoid and 18 944 first nonlymphoid malignancies were diagnosed. Risk of nonlymphoid cancer following a lymphoid malignancy was increased overall [adjusted hazard ratio (aHR) = 2.7; 95% confidence interval (CI) = 2.3–3.2], and specifically for cancers of the oral cavity (aHR = 2.6; 95% CI = 1.2–5.5), colon (2.4; 1.1–5.0), rectum (3.6; 1.9–6.7), anus (3.6; 2.5–5.1), liver (2.0; 1.2–3.5), lung (1.6; 1.1–2.4), vagina/vulva (6.1; 2.3–16.3), and central nervous system (5.0; 1.6–15.6), Kaposi sarcoma (4.6; 3.4–6.2), and myeloid malignancies (9.7; 6.1–15.4). After additional adjustment for prior AIDS diagnosis and time since HIV diagnosis, aHRs were attenuated overall (aHR = 1.7; 95% CI = 1.5–2.0) and remained significant for cancers of the rectum, anus, and vagina/vulva, Kaposi sarcoma, and myeloid malignancies.

Correspondence to Parag Mahale, PhD, 9609 Medical Center Dr, Room 6E214, Rockville, MD 20850, USA. Tel: +1 240 276 5855; parag.mahale@nih.gov.

Authorship contributions: P.M., C.U., E.A.E., and L.M.M. designed the study. E.A.E. and M.S.S., who are principal investigators in the HIV/AIDS Cancer Match Study, acquired the data and obtained funding. P.M. and C.U. conducted the statistical analyses. P.M., E.A.E., M.S.S., and L.M.M. supervised the study. All authors contributed to the interpretation of the data, critically reviewed the manuscript, and approved the final version of the manuscript.

Conflicts of interest

There are no conflicts of interest.

**Conclusion:** HIV-infected people with lymphoid malignancies have an increased risk of subsequent non-lymphoid cancers. As risks remained significant after adjustment for time since HIV diagnosis and prior AIDS diagnosis, it suggests that immunosuppression may explain some, but not all, of these risks.

### Keywords

AIDS; epidemiology; HIV infection; lymphoid malignancies; lymphoma; non-Hodgkin lymphoma; second primary cancers

## Introduction

Individuals infected with HIV have an increased cancer risk because of immunosuppression, co-infections with oncogenic viruses, such as human papillomavirus (HPV) or hepatitis viruses, and high prevalence of behaviors, such as smoking and alcohol intake that are associated with cancer risk [1]. Among HIV-infected people, risk is increased for 'AIDS-defining' cancers, which include Kaposi sarcoma, certain subtypes of non-Hodgkin lymphomas (NHLs), and cervical cancer, as well as some non-AIDS-defining cancers, such as cancers of the anus, liver, and lung, and Hodgkin lymphomas [1].

Effective combined antiretroviral therapy (cART) and treatment for lymphoid malignancies, especially AIDS-related lymphomas, have improved the survival of HIV-infected people leading to aging of this population [2,3]. As cancer risk increases with age, HIV-infected people by virtue of living longer may be diagnosed with multiple cancers over their lifetime. A recent study compared cancer risk among 22 623 people diagnosed with HIV/ AIDS in San Francisco to cancers occurring in the general population residing in geographic areas covered by nine cancer registries participating in the Surveillance, Epidemiology, and End Results (SEER) program [4]. The authors found an increased risk of not only first primary cancers but also second primary cancers, such as Kaposi sarcoma, anal cancer, liver cancer, Hodgkin lymphoma, and NHL following any first primary cancer. These findings are consistent with the known associations of HIV with these cancers. However, comparison of cancer risk following a first primary malignancy among HIV-infected people with that expected in the general population may not indicate a shared mechanism of carcinogenesis between multiple primary malignancies as the risk will be elevated for cancers associated with HIV infection.

Lymphoid malignancies, such as NHLs are some of the most common cancers that occur among HIV-infected people [1,5]. In the general population, the risk of second primary cancers is increased after lymphoid malignancies because of cancer therapy, underlying immune dysfunction, or shared risk factors (e.g. viral infections, such as HIV) [6]. However, the spectrum of cancers seen in HIV-infected people differs from that seen in the general population because of a background of HIV-induced immunosuppression [1]. Hence, cancer risk following lymphoid malignancies among HIV-infected people may not be comparable with that observed in the general population. Moreover, it is important to study cancer risk restricted to a population of HIV-infected people, thus controlling for the presence of HIV infection, to gain insights into common cause for multiple primary cancers.

The HIV/AIDS Cancer Match (HACM) Study is the largest study of cancers among HIV-infected people in the United States, and provides a unique opportunity to study cancer risk among more than 500 000 HIV-infected people [1]. Utilizing this data source, we characterized the cancer risk and patterns of second primary cancers following lymphoid malignancies among HIV-infected people to understand if HIV-infected people who develop a first primary lymphoid malignancy have an increased risk for particular subsequent cancers, and to identify cancers, which may share common etiologic factors with lymphoid malignancies.

## Methods

### Study design and participants

HIV/AIDS and cancers are both reportable diseases in the United States, and states maintain separate registries that collect data on these diseases via active and passive surveillance. HIV registries collect information on each person with HIV infection, including demographics, risk factors for HIV acquisition, dates of HIV and AIDS diagnoses and reports, AIDS-defining conditions, and date of death. Cancer registries collect data on each cancer case, including demographics; cancer diagnosis, site, and morphology; and death. The HACM Study is an ongoing study that links US population-based HIV and cancer registries (see Table 1 footnote) [1]. The study was approved by institutional review boards at participating registries as required and received exemption from review at the US National Institutes of Health.

All invasive (malignant) incident cancers among HIV-infected people were ascertained from the linked cancer registries. First primary lymphoid malignancies following HIV/AIDS diagnosis were identified using the International Classification of Diseases for Oncology, version 3 (ICD-O-3) morphology codes and the InterLymph hierarchical classification of lymphoid neoplasms for epidemiologic research based on the WHO classification [7]. Secondary analyses distinguished AIDS-defining [diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, primary central nervous system (CNS) lymphoma, B-cell lymphomas not otherwise specified, unclassified lymphomas] and non-AIDS-defining lymphoid malignancies (other types of NHL, Hodgkin lymphoma, and plasma cell neoplasms; Supplemental Table 1, http://links.lww.com/QAD/B709). We classified B-cell NHLs, not otherwise specified and unclassified NHLs as AIDS-defining lymphoid malignancies as they are likely to be DLBCLs, which is the most common lymphoid malignancy to occur among HIV-infected people [5]. We ascertained first nonlymphoid malignancies according to ICD-O-3 topography and morphology codes [8]. We could not analyze risk of keratinocytic skin cancers (squamous and basal cell carcinomas) as they are not captured by the cancer registries. We analyzed cancer risk overall, and for specific cancers with at least 100 observed cases. All other cancer types with less than 100 observed cases were combined to form the ‘Miscellaneous’ category. As rectal squamous cell carcinomas (SCCs) is a distinct clinical entity from rectal non-SCCs, and human papillomavirus (HPV)-16 could play a role in its cause [9], we analyzed risk separately for rectal SCCs and non-SCCs.

### Statistical analyses

Follow-up for cancer ascertainment began 3 months after either the start of registry coverage or HIV report date, whichever was later. When AIDS diagnosis date was earlier than the HIV report date, ascertainment began 3 months after AIDS diagnosis. Individuals in the study were censored at the time of death or end of cancer registry coverage, whichever was earlier. Including individuals with cancers diagnosed before the time of HIV report date/AIDS diagnosis date may introduce a selection bias because of left truncation in the analysis. Only individuals who develop a first cancer and have a favorable prognosis may survive long enough to be included in the study. Cancers that were diagnosed at the time of HIV diagnosis date maybe cancers that prompted HIV testing, and hence are not representative of cancers that are detected during follow-up of HIV-infected people. By allowing this 3-month lag time before the beginning of cancer ascertainment, prevalent cancer detected prior to, or at the time of HIV/AIDS diagnosis or reporting were excluded from our analysis. When a lymphoid malignancy was the reason for AIDS diagnosis and entry in the cohort, such people were considered to have prevalent cancers and excluded from analysis.

First, to describe lymphoma risk factors in our study population, we analyzed risk of any first primary lymphoid malignancy among HIV-infected people. We performed Cox proportional hazards regression using age as the time scale and included in the model a priori variables for sex/risk group [men who have sex with men (MSM), male injection drug user (IDU), MSM/IDU, male other/unknown, female IDU, female other unknown], race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other/multiple/unknown), calendar year of cohort entry, and prior AIDS diagnosis and time since HIV diagnosis as time-dependent covariates. We present the adjusted hazard ratios (aHRs) and their corresponding 95% confidence intervals (CIs). The follow-up for this analysis was terminated at the earliest of first lymphoid malignancy diagnosis or censoring date (as described above).

We then assessed the risk of first nonlymphoid cancers following a lymphoid malignancy using Cox proportional hazards regression model with age as the time scale. We used lymphoid malignancy diagnosis as a time-dependent variable and terminated the follow-up at the earliest of first nonlymphoid malignancy diagnosis or censoring date. Initial models (Model 1) were adjusted for sex/risk group, race/ethnicity, and calendar year of cohort entry with age as the time scale. We additionally adjusted for prior AIDS diagnosis and time since HIV diagnosis as time-dependent variables (Model 2), the former representing the onset of pronounced immunosuppression. The proportional hazards assumption was tested by introducing an interaction term of the exposure variable with log of follow-up time in the Cox models and $P$ less than 0.05 for the interaction term was considered a violation of the assumption.

We conducted additional analyses for cancers where there were at least five second primary cancers. To assess potential differences in cancer risk associated with different types of lymphoid malignancies, we analyzed cancer risk separately following first AIDS-defining or non-AIDS-defining lymphoid malignancies, and following first NHLs, Hodgkin lymphoma, or plasma cell neoplasm. Extensive radiologic/laboratory investigations shortly after

lymphoid malignancy diagnosis may lead to detection of incidental cancers. Furthermore, a lymphoid malignancy in an HIV-infected person may indicate deteriorated immune function around the time of diagnosis. We, therefore, assessed cancer risk according to whether cancers were diagnosed 6 months or less or more than 6 months after the lymphoid malignancy diagnosis and evaluated the effect of adjusting for AIDS diagnosis and time since HIV diagnosis. We also evaluated cancer risk according to the stage at nonlymphoid cancer diagnosis. As $CD4^+$ count data were not complete in our study, we conducted an exploratory analysis wherein we evaluated $CD4^+$ counts within 6 months before and after a lymphoid malignancy diagnosis and classified first primary cancers as lymphoid malignancy with $CD4^+$ cell counts 200 cells/μl or less, $CD4^+$ cell counts greater than 200 cells/μl, and $CD4^+$ cell counts missing. We then analyzed risk of subsequent nonlymphoid malignancies as described above. We did all statistical analyses with SAS (version 9.3; SAS Institute, Cary, North Carolina, USA).

## Results

We included 531 460 HIV-infected people in our study. Most participants were less than 50 years of age at the start of follow-up (83.7%), men (72.4%), most commonly MSM (35.1%), and non-Hispanic black (50.0%) (Table 1). During the follow-up, 6513 first lymphoid malignancies were diagnosed. Most lymphoid malignancies were AIDS-defining (*N* = 4542; 69.7%), most commonly DLBCLs (*N* = 2461; 37.8%) (Supplemental Table 1, http://links.lww.com/QAD/B709). The remaining 1971 lymphoid malignancies constituted non-AIDS-defining NHLs (*N* = 576; 8.8%), Hodgkin lymphomas (*N* = 1,130; 17.3%), and plasma cell neoplasms (*N* = 265;4.1%). Risk of any first lymphoid malignancy was increased among MSM, non-Hispanic whites, participants with prior AIDS diagnoses, those who entered the cohort between 1996 and 2000, and within 5 years of HIV diagnosis (Table 1).

Compared with HIV-infected people without lymphoid malignancy, those who had any lymphoid malignancy diagnosis had an increased risk of subsequent nonlymphoid cancer (aHR = 2.7; 95% CI = 2.3–3.2) (Table 2, Supplemental Table 2, http://links.lww.com/QAD/B709). In minimally adjusted models (Model 1), risk was specifically increased for cancers of the oral cavity (aHR = 2.6; 95% CI = 1.2–5.5), colon (aHR = 2.4; 95% CI = 1.1–5.0), rectum (aHR = 3.6; 95% CI = 1.9–6.7), anus (aHR = 3.6; 95% CI = 2.5–5.1), liver (aHR = 2.0; 95% CI = 1.2–3.5), lung (aHR = 1.6; 95% CI = 1.1–2.4), vagina/vulva (aHR = 6.1; 95% CI = 2.3–16.3), and central nervous system (CNS; aHR = 5.0; 95% CI = 1.6–15.6), Kaposi sarcoma (aHR = 4.6; 95% CI = 3.4–6.2), myeloid malignancies (aHR = 9.7; 95% CI = 6.1–15.4), and miscellaneous cancers (aHR = 3.4; 95% CI = 2.1–5.3). Risk for both rectal SCC (*N* = 163; aHR = 5.5; 95% CI = 2.3–13.5) and non-SCC (*N* = 386; aHR = 2.7; 95% CI = 1.1–6.5) was elevated following any lymphoid malignancy.

After adjusting for prior AIDS diagnosis and time since HIV diagnosis (Model 2), the aHRs were attenuated overall (aHR = 1.7; 95% CI = 1.5–2.0) and for each cancer, and they were no longer significant for cancers of the oral cavity (aHR = 1.9; 95% CI = 0.9–4.0), colon (aHR = 2.0; 95% CI = 1.0–4.3), rectal non-SCC (aHR = 2.0; 95% CI = 0.8–4.9), liver (aHR = 1.7; 95% CI = 1.0–3.0), lung (aHR = 1.2; 95% CI = 0.8–1.8), and CNS (aHR = 3.2; 95%

CI = 1.0–10.2) (Table 2, Supplemental Table 2, http://links.lww.com/QAD/B709). Notably, the aHRs attenuated by more than 50% for Kaposi sarcoma (from aHR = 4.6 to aHR = 2.0).

Risk estimates presented for cancer risk following different types of lymphoid malignancies were derived from Model 2. Overall cancer risk was increased following both AIDS-defining (aHR = 1.7; 95% CI = 1.5–2.0) and non-AIDS-defining lymphoid malignancies (aHR = 2.0; 95% CI = 1.6–2.5) (Table 3). Risk of oral cavity, colon, anus, and miscellaneous cancers, Kaposi sarcoma, and myeloid malignancies was significantly increased after an AIDS-defining lymphoid malignancy, whereas risk of rectal, anus, and female breast cancers, and myeloid malignancies was significantly increased after non-AIDS-defining lymphoid malignancies. Cancer risk was also elevated following any first NHL (aHR = 1.8; 95% CI = 1.6–2.1), Hodgkin lymphoma (aHR = 1.9; 95% CI = 1.4–2.5), or plasma cell neoplasm (aHR = 2.1; 95% CI = 1.2–3.5) (Supplemental Table 3, http://links.lww.com/QAD/B709). Specifically, risk of oral cavity, colon, kidney, and miscellaneous cancers, and Kaposi sarcoma was increased following any NHL, whereas risk of rectal cancer was increased following Hodgkin lymphoma. Risk of anal cancer and myeloid malignancies was increased following both NHL and Hodgkin lymphoma. Specific cancer risk following plasma cell neoplasms could not be evaluated because of small number of second primary cancers.

Cancer risk overall was increased at both 6 or less or more than 6 months after lymphoid malignancy (Table 4). The median time from the diagnosis of first lymphoid malignancy to the first nonlymphoid malignancy was 90 days (interquartile range, 31–122 days) for cancer diagnosed at 6 months or less after lymphoid malignancy, and 3.8 years (interquartile range, 1.8–5.9 years) for cancers diagnosed at more than 6 months after lymphoid malignancy. Adjustment for prior AIDS diagnosis and time since HIV diagnosis resulted in greater attenuation in the aHRs for cancers occurring 6 months or less after lymphoid malignancy diagnosis (Model 1, aHR = 7.3; Model 2, aHR = 2.7) compared with more than 6 months after lymphoid malignancy diagnosis (Model 1, aHR = 1.8; Model 2, aHR = 1.5). Risk was particularly increased for cancers of the colon, rectum (non-SCC), anus, lung, kidney, and miscellaneous sites, and Kaposi sarcoma 6 months or less after lymphoid malignancy diagnosis, and these risks were attenuated in fully adjusted models. In contrast, risk was increased for cancers of the oral cavity, rectum (SCC), anus, liver, and miscellaneous sites, and myeloid malignancies more than 6 months after lymphoid malignancy diagnosis and was not attenuated in fully adjusted models.

In analyses by nonlymphoid cancer stage at diagnosis, risks were significant for localized/stage I cancers but not regional/distant/stage II–IV cancers for rectum (aHR = 4.4), liver (aHR = 3.6), and lung cancers (aHR = 3.0) (Supplemental Table 4, http://links.lww.com/QAD/B709). Among 6513 HIV-infected people who developed a lymphoid malignancy, 2117 (32.5%) had missing $CD4^+$ cell count data (Supplemental Table 5, http://links.lww.com/QAD/B709). Risk of any nonlymphoid malignancy was higher among people who developed a lymphoid malignancy compared with those who did not, irrespective of whether the $CD4^+$cell count was 200 cells/ml or less (aHR = 2.7), greater than 200 cells/μl (aHR = 2.0), or missing (aHR = 2.6) at the time of lymphoid malignancy diagnosis (Supplemental Table 6, http://links.lww.com/QAD/B709). Evaluation of cancer risk

following lymphoid malignancy with $CD4^+$ cell count 200 or less vs. greater than 200 cells/μl was limited because of small numbers; a notable exception was increased risk of Kaposi sarcoma (aHR = 3.2; 95% CI = 1.2–8.2).

## Discussion

In an analysis of data from a large registry-based linkage study, we found that HIV-infected people who develop lymphoid malignancies have an increased risk of subsequent nonlymphoid cancers, specifically cancers of the oral cavity, colon, rectum, anus, liver, lung, vagina/vulva, CNS, Kaposi sarcoma, and myeloid malignancies. Attenuation of the strength of these associations after adjustment for AIDS diagnosis and time since HIV diagnosis indicates a common role for immunosuppression in the cause of some of these cancers. The lack of attenuation of risk estimates at more than 6 months after lymphoid malignancy for some cancers implicates presence of shared risk factors other than immunosuppression or the effect of treatment for lymphoid malignancies. Healthcare providers involved in medical care of HIV-infected people should be aware of the possibility of second primary cancer diagnosis following a diagnosis of lymphoid malignancy and restoration of immune function and maintaining virologic control with cART should continue to remain a priority in the clinical management of HIV infection.

HIV-infected people have an increased risk of virus-related cancers, such as those caused by HPV (anogenital cancers), hepatitis viruses (liver cancer), Epstein-Barr virus (EBV) (some lymphomas), and human herpesvirus 8 (Kaposi sarcoma) [10,11]. In our study, risk of infection-related cancers, such as anal, liver, and vaginal/vulvar cancers, and Kaposi sarcoma were increased following lymphoid malignancies. Rectal SCC is a distinct clinical entity from anal SCC and HPV-16 may play an etiologic role in the development of this cancer, which explains the strong risk of rectal SCC following lymphoid malignancies [12]. Risk of rectal SCC, anus, and liver cancer was increased at more than 6 months after lymphoid malignancy. Chemotherapy for treating lymphoid neoplasms may enhance viral replication and promote carcinogenesis. For example, chronic hepatitis B and C viral reactivation and hepatitis flares have been reported in patients with lymphoid malignancies receiving rituximab-containing regimens [13–15] and immunosuppressive drugs are known to increase risk of HPV-related cancers among solid organ transplant recipients [16].

Immunosuppression induced by HIV infection plays an important role in cancer development, particularly lymphoid malignancies, and some of them (such as DLBCL, Burkitt lymphoma, and primary CNS lymphoma) signify the onset of AIDS [17]. Thus, the occurrence of lymphoid malignancies indicates worsened immune status of the person and increases the risk of cancers associated with immunosuppression [17]. Furthermore, treatment for lymphoid malignancies, such as DLBCL include multidrug chemotherapeutic regimens, which may lead to immunosuppression and increase subsequent cancer risk. Notably, in our study, the risk of Kaposi sarcoma, an AIDS-defining cancer, was highly increased following an AIDS-defining lymphoid malignancy, and within the first 6 months of the lymphoid malignancy diagnosis. Attenuation in the aHRs after adjusting for markers of immunosuppression within this time frame suggest that immunosuppression may play a greater role in increasing cancer risk within the first 6 months after lymphoid malignancy

diagnosis. Risk of Kaposi sarcoma was also increased following lymphoid malignancy associated with low $CD4^+$ cell count.

Increased risk of cancers only within 6 months after lymphoid malignancy diagnosis may indicate surveillance bias. HIV-infected people diagnosed with lymphoid malignancies may undergo extensive investigation with radiological methods like PET scans that may lead to diagnosis of incidental cancers. Risk of lung cancer was increased only for localized/stage I cancers and within 6 months after lymphoid malignancy suggesting a possibility of enhanced surveillance leading to detection of incidental cancers. Smoking is a risk factor for oral cavity cancer, lung cancer, and possibly some NHLs [18,19]. This common risk factor may explain increased risk of oral cavity and lung cancers following lymphoid malignancies. People diagnosed with lymphoid malignancies are likely to receive intense chemotherapy with alkylating agents and topoisomerase II inhibitors, which are known to cause DNA damage and increase the risk for myeloid malignancies [9,20–22]. Increased risk of myeloid malignancies following DLBCL in the general population has been reported previously, which may explain a similar observation in our cohort of HIV-infected people [6].

A strength of our study was leveraging the data linkage between HIV and cancer registries, which allowed us to systematically ascertain second cancer risk among more than 500 000 HIV-infected people, which were representative of the US HIV population. Cancer registries have high-quality control for their cancer ascertainment, which improved the validity of our cancer outcomes. Our study did have some limitations that are inherent in the analyses of large registry-based data. We lacked information on HIV viral load or cARTuse, which are important markers of immune status. Though we analyzed data on $CD4^+$ count, it was missing in a large proportion of cases. Instead, we relied on AIDS diagnosis and time since HIV diagnosis, which may lead to residual confounding. Prior AIDS diagnosis is an indicator of ever having profound immunosuppression, while time since HIV diagnosis may to some extent capture entry into care and cARTuse (as lymphoid malignancy risk decreased with greater duration). These variables are not perfect indicators of the magnitude of immunosuppression, particularly in the cARTera where more than 80% of people in medical care had achieved viral suppression [23]. We also lacked data on important cancer risk factors, such as viral coinfections and smoking, which precluded us from assessing their role in increasing risk of some cancers. As we began cancer risk assessment at 3 months following cohort entry, we may have missed some cancer cases. It is also possible that people may have moved out of the cancer registry catchment area and developed cancers that we may have missed. Ann Arbor stage and grade of lymphomas affect cancer prognosis and may affect risk of subsequent cancers. However, we did not have data on the stage of lymphomas. Analyzing cancer risk according to different grades of lymphomas was not possible because of small number of lymphoid malignancies in our cohort. Treatment for lymphoid malignancies can affect cancer risk by causing immunosuppression or DNA damage. However, we did not have data on treatment and could not evaluate its effect on subsequent cancer risk. Finally, we had a small number of certain second primary cancers, which affected the precision of our estimates.

Immunosuppression plays a major role in increasing cancer risk, including second primary cancers, among HIV-infected people. The diagnosis of a lymphoid malignancy may indicate

worsening immune status and clinicians managing HIV-infected people should be aware of the possibility of a subsequent cancer diagnosis. Therefore, restoration of immune function with cART should continue to remain the primary focus in the clinical management of HIV-infected people. Treatment for lymphoid malignancies may increase the risk of subsequent myeloid malignancies. As some cancers may have longer latency periods, there should be increased focus on primary prevention measures, such as HPV and hepatitis B vaccination, and smoking cessation. Screening for cervical, anal, and liver cancers may lead to identification of cancers at an earlier stage, but the benefits need to be weighed with risks associated with overdiagnosis and treatment-related adverse effects.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

We acknowledge the support and assistance provided by individuals at the following USA HIV/AIDS and cancer registries: Colorado, Connecticut, Georgia, Maryland, Michigan, New Jersey, New York, North Carolina, Puerto Rico, and Texas. We also thank Timothy S. McNeel at Information Management Services for programming support.

The views expressed in this article are those of the authors and should not be interpreted to reflect the views or policies of the National Cancer Institute, HIV/AIDS or cancer registries, or their contractors. This research was supported in part by the Intramural Research Program of the National Cancer Institute.

The following cancer registries were supported by the SEER Program of the National Cancer Institute: Connecticut (HHSN261201300019I) and New Jersey (HHSN261201300021I, N01-PC-2013-00021). The following cancer registries were supported by the National Program of Cancer Registries of the Centers for Disease Control and Prevention: Colorado (NU58DP006347-01), Georgia (5U58DP003875-01), Maryland (5NU58DP003919-05-00), Michigan (5U58DP003921-03), New Jersey (NU58/DP003931-05-00), New York (U58/DP003879), North Carolina (1NU58DP006281), and Texas (5U58DP000824-04). The New Jersey State Cancer Registry was also supported by the state of New Jersey, the Maryland Cancer Registry was supported by the State of Maryland and the Maryland Cigarette Restitution Fund, and the New York State Cancer Registry was also supported by the state of New York. The following HIV registries were supported by HIV Incidence and Case Surveillance Branch of the Centers for Disease Control and Prevention, National HIV Surveillance Systems: Colorado (NU62PS003960), Connecticut (5U62PS001005-05), Michigan (U62PS004011-02), and New Jersey (U62PS004001-2).

Sources of funding: This research was supported in part by the Intramural Research Program of the National Cancer Institute.

C.U. was supported by NIH F31 CA246855 and T32 CA009314 training grants.

## References

1. Hernandez-Ramirez RU, Shiels MS, Dubrow R, Engels EA. Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study. Lancet HIV 2017; 4:e495–e504. [PubMed: 28803888]
2. Mahale P, Engels EA, Coghill AE, Kahn AR, Shiels MS. Cancer risk in older persons living with human immunodeficiency virus infection in the United States. Clin Infect Dis 2018; 67:50–57. [PubMed: 29325033]
3. Dunleavy K, Wilson WH. How I treat HIV-associated lymphoma. Blood 2012; 119:3245–3255. [PubMed: 22337719]
4. Hessol NA, Whittemore H, Vittinghoff E, Hsu LC, Ma D, Scheer S, Schwarcz SK. Incidence of first and second primary cancers diagnosed among people with HIV, 1985–2013: a population-based, registry linkage study. **Lancet***HIV* 2018; 5:e647–e655.

5. Gibson TM, Morton LM, Shiels MS, Clarke CA, Engels EA. Risk of non-Hodgkin lymphoma subtypes in HIV-infected people during the HAART era: a population-based study. Aids 2014; 28:2313–2318. [PubMed: 25111081]
6. Morton LM, Curtis RE, Linet MS, Bluhm EC, Tucker MA, Caporaso N, et al. Second malignancy risks after non-Hodgkin's lymphoma and chronic lymphocytic leukemia: differences by lymphoma subtype. J Clin Oncol 2010; 28:4935–4944. [PubMed: 20940199]
7. Turner JJ, Morton LM, Linet MS, Clarke CA, Kadin ME, Vajdic CM, et al. InterLymph hierarchical classification of lymphoid neoplasms for epidemiologic research based on the WHO classification (2008): update and future directions. Blood 2010; 116:e90–e98. [PubMed: 20699439]
8. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975–2016, National Cancer Institute. Bethesda, MD Available at: https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site, April 2019.
9. Andre M, Mounier N, Leleu X, Sonet A, Brice P, Henry-Amar M, et al. Second cancers and late toxicities after treatment of aggressive non-Hodgkin lymphoma with the ACVBP regimen: a GELA cohort study on 2837 patients. Blood 2004; 103:1222–1228. [PubMed: 14576060]
10. de Martel C, Shiels MS, Franceschi S, Simard EP, Vignat J, Hall HI, et al. Cancers attributable to infections among adults with HIV in the United States. Aids 2015; 29:2173–2181. [PubMed: 26182198]
11. Riedel DJ, Tang LS, Rositch AF. The role of viral co-infection in HIV-associated non-AIDS-related cancers. **Curr HIV/AIDS***Rep* 2015; 12:362–372.
12. Coghill AE, Bellizzi AM, Lynch CF, Shiels MS, Selk FR, Gillison M, et al. Pathology characterization and detection of human papillomavirus type 16 in rectal squamous cell carcinomas. **Clin Gastroenterol***Hepatol* 2019; 17:2129–2131.
13. Seto WK, Chan TS, Hwang YY, Wong DK, Fung J, Liu KS, et al. Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study. J Clin Oncol 2014; 32:3736–3743. [PubMed: 25287829]
14. Torres HA, Hosry J, Mahale P, Economides MP, Jiang Y, Lok AS. Hepatitis C virus reactivation in patients receiving cancer treatment: a prospective observational study. Hepatology 2018; 67:36–47. [PubMed: 28653760]
15. Loomba R, Liang TJ. Hepatitis B reactivation associated with immune suppressive and biological modifier therapies: current concepts, management strategies, and future directions. Gastroenterology 2017; 152:1297–1309. [PubMed: 28219691]
16. Madeleine MM, Finch JL, Lynch CF, Goodman MT, Engels EA. HPV-related cancers after solid organ transplantation in the United States. Am J Transplant 2013; 13:3202–3209. [PubMed: 24119294]
17. Hernandez-Ramirez RU, Qin L, Lin H, Leyden W, Neugebauer RS, Althoff KN, et al. Association of immunosuppression and HIV viraemia with non-Hodgkin lymphoma risk overall and by subtype in people living with HIV in Canada and the USA: a multicentre cohort study. Lancet HIV 2019; 6:e240–e249. [PubMed: 30826282]
18. Agudo A, Bonet C, Travier N, Gonzalez CA, Vineis P, Bueno-de-Mesquita HB, et al. Impact of cigarette smoking on cancer risk in the European prospective investigation into cancer and nutrition study. J Clin Oncol 2012; 30:4550–4557. [PubMed: 23169508]
19. Morton LM, Hartge P, Holford TR, Holly EA, Chiu BC, Vineis P, et al. Cigarette smoking and risk of non-Hodgkin lymphoma: a pooled analysis from the International Lymphoma Epidemiology Consortium (interlymph). **Cancer Epidemiol***Biomarkers* Prev 2005; 14:925–933.
20. McLaughlin P, Estey E, Glassman A, Romaguera J, Samaniego F, Ayala A, et al. Myelodysplasia and acute myeloid leukemia following therapy for indolent lymphoma with fludarabine, mitoxantrone, and dexamethasone (FND) plus rituximab and interferon alpha. Blood 2005; 105:4573–4575. [PubMed: 15741224]
21. Moser EC, Noordijk EM, van Leeuwen FE, Baars JW, Thomas J, Carde P, et al. Risk of second cancer after treatment of aggressive non-Hodgkin's lymphoma; an EORTC cohort study. Haematologica 2006; 91:1481–1488. [PubMed: 17043014]

22. Mudie NY, Swerdlow AJ, Higgins CD, Smith P, Qiao Z, Hancock BW, et al. Risk of second malignancy after non-Hodgkin's lymphoma: a British Cohort Study. J Clin Oncol 2006; 24:1568–1574. [PubMed: 16520465]

23. Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas. HIV Surveillance Suppl Rep 2016; 23:5–8.

*AIDS*. Author manuscript; available in PMC 2021 July 01.

**Table 1.**

Characteristics of the study population and risk factors for lymphoid malignancies.

| Characteristics | Total number of HIV-infected people, n (column%) *N*=531 460 | Number with first primary lymphoid malignancies, n (row %) *N*=6513 | aHR (95% CI)[a] |
|---|---|---|---|
| Age at the start of follow-up (years)[b] | | | |
| <30 | 108 564 (20.4) | 916 (0.8) | … |
| 30–39 | 169 265 (31.9) | 2299 (1.4) | … |
| 40–49 | 166 995 (31.4) | 2236 (1.3) | … |
| 50–59 | 67 797 (12.8) | 820 (1.2) | … |
| ≥60 | 18 839 (3.5) | 242 (3.7) | … |
| Sex/risk group | | | |
| MSM | 186 606 (35.1) | 2481 (1.3) | Ref |
| Male IDU | 64 351 (12.1) | 839 (1.3) | 0.7 (0.7–0.8) |
| MSM/ IDU | 21 956 (4.1) | 323 (1.5) | 0.9 (0.8–1.1) |
| Male other/unknown | 112 168 (21.1) | 1432 (1.3) | 0.8 (0.8–0.9) |
| Female IDU | 32 230 (6.1) | 321 (1.0) | 0.6 (0.5–0.7) |
| Female other/unknown | 114 149 (21.5) | 1117 (1.0) | 0.8 (0.7–0.8) |
| Race/ethnicity | | | |
| Non-Hispanic white | 123 091 (23.2) | 1751 (1.4) | Ref |
| Non-Hispanic black | 265 576 (50.0) | 2912 (1.1) | 0.9 (0.8–0.9) |
| Hispanic | 133 316 (25.0) | 1761 (1.3) | 1.1 (1.0–1.1) |
| Other/multiple/unknown | 9477 (1.8) | 89 (0.9) | 0.9 (0.7–1.1) |
| Prior AIDS diagnosis[c] | | | |
| No | 203 978 (38.4) | 1408 (0.7) | Ref |
| Yes | 327 482 (61.6) | 5105 (1.6) | 2.4 (2.2–2.5) |
| Calendar year of cohort entry | | | |
| 1996–2000 | 98289 (18.5) | 2143 (2.2) | Ref |
| 2001–2003 | 152 668 (28.7) | 2305 (1.5) | 0.8 (0.7–0.8) |
| 2004–2007 | 126 586 (23.8) | 1308 (1.0) | 0.4 (0.3–0.4) |
| 2008–2015 | 153 917 (29.0) | 757 (0.5) | 0.1 (0.1–0.1) |
| Time since HIV diagnosis (years)[c] | | | |

| Characteristics | Total number of HIV-infected people, n (column%) *N*=531 460 | Number with first primary lymphoid malignancies, n (row %) *N*=6513 | aHR (95% CI)[a] |
|---|---|---|---|
| 0–4.9 | 112 064 (21.1) | 2,310 (2.1) | Ref |
| 5–9.9 | 127 004 (23.9) | 1675 (1.3) | 0.1 (0.1–0.1) |
| >10 | 228 625 (43.0) | 1720 (0.8) | 0.02 (0.02–0.02) |
| Missing | 63 767 (12.0) | 808 (1.3) | 0.04 (0.03–0.04) |

The number of cancers for time-dependent variables (age categories, prior AIDS diagnosis, and time since HIV diagnosis) are shown for when the cancers occurred. Cancer registries included in the study (years of coverage): Colorado (1998–2015), Connecticut (2005–10), Georgia (2004–12), Maryland (2008–12), Michigan (1996–2010), New Jersey (1996–2012), New York (2001–12), North Carolina (1996–2014), Puerto Rico (2003–12), and Texas (1999–2015). aHR, adjusted hazard ratio; CI, confidence intervals; IDU, injection drug users; MSM, men who have sex with men.

[a]Adjusted for sex/risk group, race/ethnicity, calendar year of cohort entry, and prior AIDS diagnosis and time since HIV diagnosis as time-varying covariates.

[b]Age was used as the time scale in Cox regression models, so aHRs are not shown.

[c]Prior AIDS diagnosis and time since HIV diagnosis were used as time-varying covariates.

**Table 2.**

Cancer risk following lymphoid malignancies among HIV-infected people.

| Cancers | Number of cancers (*N*) | Number with first primary lymphoid malignancies [*N* (row %)] | aHR (95% CI) Model 1[a] | aHR (95% CI) Model 2[a] |
|---|---|---|---|---|
| Any first nonlymphoid cancer | 18 944 | 226 (1.2) | **2.7 (2.3–3.2)** | **1.7 (1.5–2.0)** |
| Oral cavity | 511 | 7 (1.4) | **2.6 (1.2–5.5)** | 1.9 (0.9–4.0) |
| Colon | 601 | 7 (1.2) | **2.4 (1.1 −5.0)** | 2.0 (1.0–4.3) |
| Rectum | 549 | 10 (1.8) | **3.6 (1.9–6.7)** | **2.7 (1.5–5.1)** |
| Rectal SCC | 163 | 5 (3.1) | **5.5 (2.3–13.5)** | **4.1 (1.7–10.1)** |
| Rectal non-SCC | 386 | 5 (1.3) | **2.7 (1.1 −6.4)** | 2.0 (0.8–4.9) |
| Anus | 1744 | 32 (1.8) | **3.6 (2.5–5.1)** | 2.6 (1.8–3.6) |
| Liver | 1377 | 13 (0.9) | **2.0 (1.2–3.5)** | 1.7 (1.0–3.0) |
| Lung | 3111 | 24 (0.8) | **1.6 (1.1 −2.4)** | 1.2 (0.8–1.8) |
| Kaposi sarcoma | 2379 | 44 (1.9) | **4.6 (3.4–6.2)** | **2.0 (1.5–2.7)** |
| Female breast | 873 | 5 (0.6) | 1.7 (0.7–4.1) | 1.4 (0.6–3.4) |
| Prostate | 1803 | 7 (0.4) | 0.7 (0.3–1.4) | 0.6 (0.3–1.3) |
| Kidney | 441 | 5 (1.1) | 2.4 (1.0–5.7) | 2.0 (0.8–4.9) |
| Myeloid malignancies[b] | 447 | 19 (4.3) | **9.7 (6.1–15.4)** | **7.1 (4.5–11.3)** |
| Miscellaneous[c] | 1237 | 19 (1.5) | **3.4 (2.1 −5.3)** | **2.5 (1.6–3.9)** |

Highlighted aHRs and 95% CIs indicate estimates that were statistically significant with *P* less than 0.05. Estimates for risk of all evaluated nonlymphoid cancers including those with less than five previous lymphoid malignancies are provided in Supplemental Table 2. Model 2: models adjusted for sex/risk group, race/ethnicity, calendar year of cohort entry, and prior AIDS diagnosis and time since HIV diagnosis as time-varying covariates. Models 1 and 2 had age as the time scale. aHR, adjusted hazard ratio; CI, confidence interval; SCC, squamous cell carcinoma.

[a]Model 1: models adjusted for sex/risk group, race/ethnicity, and calendar year of cohort entry.

[b]Myeloid malignancies include myelodysplasia, myeloproliferative neoplasms, and other myeloid malignancies.

[c]Miscellaneous cancers include cancers of the following sites: salivary glands (*N* = 32), other oral cavity/pharynx (*N* = 85), small intestine (*N* = 70), other gastrointestinal tract (*N* = 33), other respiratory tract (*N* = 49), bone and cartilage (*N* = 77), male breast (*N* = 32), other female genital tract (*N* = 88), other male genital tract (*N* = 25), eye and orbit (*N* = 39), other urinary tract (*N* = 21), other endocrine glands (*N* = 26), and unknown primary site (*N* = 660).

**Table 3.**

Cancer risk following AIDS-defining and non-AIDS-defining lymphoid malignancies among HIV-infected people.

| | | AIDS-defining lymphoid malignancy | | Non-AIDS-defining lymphoid malignancy | |
|---|---|---|---|---|---|
| **Cancers** | **Number of cancers (*N*)** | **Number with first primary lymphoid malignancies N (row %)** | **aHR (95% CI)[a]** | **Number with first primary lymphoid malignancies [*N* (row %)]** | **aHR (95% CI)[a]** |
| Any first nonlymphoid cancer | 18 944 | 139 (0.7) | **1.7 (1.5–2.0)** | 87 (0.5) | **2.0 (1.6–2.5)** |
| Oral cavity | 511 | 6 (1.2) | **2.4 (1.1 −5.4)** | 1 (0.2) | ... |
| Colon | 601 | 5 (0.8) | **2.5 (1.0–6.0)** | 2 (0.3) | ... |
| Rectum | 549 | 3 (0.6) | 1.2 (0.4–3.8) | 7 (1.3) | **5.5 (2.6–11.6)** |
| Anus | 1744 | 16 (0.9) | **1.9 (1.1 −3.1)** | 16 (0.9) | **4.0 (2.4–6.6)** |
| Liver | 1377 | 7 (0.5) | 1.5 (0.7–3.2) | 6 (0.4) | 2.1 (0.9–4.6) |
| Lung | 3111 | 13 (0.4) | 1.1 (0.6–1.8) | 11 (0.4) | 1.5 (0.8–2.7) |
| Kaposi sarcoma | 2379 | 37 (1.6) | **2.3 (1.6–3.1)** | 7 (0.3) | 1.3 (0.6–2.8) |
| Female breast | 873 | 1 (0.1) | … | 4 (0.5) | **2.8 (1.1 −7.5)** |
| Prostate | 1803 | 1 (0.1) | … | 6 (0.3) | 1.3 (0.6–2.8) |
| Kidney | 441 | 4 (0.9) | 2.6 (1.0–7.1) | 1 (0.2) | ... |
| Myeloid malignancies[b] | 447 | 11 (2.5) | **6.2 (3.4–11.3)** | 8 (1.8) | **8.3 (4.1–16.8)** |
| Miscellaneous[c] | 1237 | 16 (1.3) | **3.2 (2.0–5.3)** | 3 (0.2) | 1.1 (0.4–3.4) |

Highlighted aHRs and 95% CIs indicate estimates that were statistically significant with $P < 0.05$. (…) Hazard ratios were suppressed for comparisons when there were ≤2 nonlymphoid cancers with prior lymphoid malignancies. Cox regression models had age as the time scale. aHR, adjusted hazard ratio; CI, confidence interval.

[a]Models adjusted for sex/risk group, race/ethnicity, calendar year of cohort entry, and prior AIDS diagnosis and time since HIV diagnosis as time-varying covariates.

[b]Myeloid malignancies include myelodysplasia, myeloproliferative neoplasms, and other myeloid malignancies.

[c]Miscellaneous cancers include cancers of the following sites: salivary glands (*N* = 32), other oral cavity/pharynx (*N* = 85), small intestine (*N* = 70), other gastrointestinal tract (*N* = 33), other respiratory tract (*N* = 49), bone and cartilage (*N* = 77), male breast (*N* = 32), other female genital tract (*N* = 88), other male genital tract (*N* = 25), eye and orbit (*N* = 39), other urinary tract (*N* = 21), other endocrine glands (*N* = 26), and unknown primary site (*N* = 660).

**Table 4.**

Cancer risk following first lymphoid malignancy by latency period (≤ 6 months or >6 months after lymphoid malignancy).

| Cancers | Number of cancers (*N*) | 6 months or less after first primary lymphoid malignancy diagnosis | | | More than 6 months after first primary lymphoid malignancy diagnosis | | |
|---|---|---|---|---|---|---|---|
| | | Number with first primary lymphoid malignancies N (row %) | aHR (95% CI) Model 1[a] | aHR (95% CI) Model 2[a] | No. with first primary lymphoid malignancies [*N* (row %)] | aHR (95% CI) Model 1[a] | aHR (95% CI) Model 2[a] |
| Any nonlymphoid malignancy | 18 944 | 84 (0.4) | **7.3 (5.9–9.1)** | **2.7 (2.2–3.4)** | 142 (0.7) | **1.8 (1.6–2.2)** | **1.5 (1.3–1.8)** |
| Oral cavity | 511 | 0 (0) | … | … | 7 (1.4) | **2.9 (1.4–6.2)** | **2.5 (1.2–5.2)** |
| Colon | 601 | 4 (0.7) | **11.0 (4.1–29.5)** | **5.4 (2.0–14.6)** | 3 (0.5) | 1.2 (0.4–3.6) | 1.1 (0.4–3.5) |
| Rectum | 549 | 2 (0.4) | **…** | **…** | 8 (1.5) | **3.3 (1.6–6.6)** | **2.8 (1.4–5.6)** |
| Anus | 1744 | 9 (0.5) | **7.9 (4.1–15.3)** | **3.4 (1.8–6.5)** | 23 (1.3) | **3.0 (2.0–4.5)** | **2.4 (1.6–3.5)** |
| Liver | 1377 | 1 (<0.1) | **…** | **…** | 12 (0.9) | **2.1 (1.2–3.8)** | **2.0 (1.1 −3.5)** |
| Lung | 3111 | 10 (0.3) | **5.5 (3.0–10.2)** | **2.1 (1.2–4.0)** | 14 (0.5) | 1.1 (0.6–1.8) | 0.9 (0.6–1.6) |
| Kaposi sarcoma | 2379 | 36 (1.5) | **24.4 (17.5–33.9)** | **4.4 (3.2–6.1)** | 8 (0.3) | 1.0 (0.5–2.0) | 0.6 (0.3–1.2) |
| Female breast | 873 | 1 (0.1) | … | … | 4 (0.5) | 1.6 (0.6–4.2) | 1.6 (0.6–4.1) |
| Prostate | 1803 | 1 (<0.1) | … | … | 6 (0.3) | 0.6 (0.3–1.4) | 0.6 (0.3–1.4) |
| Kidney | 441 | 2 (0.5) | … | … | 3 (0.7) | 1.6 (0.5–5.1) | 1.6 (0.5–4.9) |
| Myeloid malignancies[b] | 447 | 1 (0.2) | … | … | 18 (4.0) | **10.6 (6.6–17.0)** | **9.1 (5.6–14.6)** |
| Miscellaneous[c] | 1237 | 5 (0.4) | **6.8 (2.8–16.4)** | **2.5 (1.1 −6.1)** | 14 (1.1) | **2.8 (1.7–4.8)** | **2.4 (1.4–4.1)** |

Highlighted aHRs and 95% CIs indicate estimates that were statistically significant with $P < 0.05$. (…) Hazard ratios were suppressed for comparisons when there were less than two nonlymphoid cancers with prior lymphoid malignancies. Model 2: models adjusted for sex/risk group, race/ethnicity, calendar year of cohort entry, and prior AIDS diagnosis and time since HIV diagnosis as time-varying covariates. Models 1 and 2 had age as the time scale. aHR, adjusted hazard ratio; CI, confidence interval.

[a]Model 1: Models adjusted for sex/risk group, race/ethnicity, and calendar year of cohort entry.

[b]Myeloid malignancies include myelodysplasia, myeloproliferative neoplasms, and other myeloid malignancies.

[c]Miscellaneous cancers include cancers of the following sites: salivary glands (*N* = 32), other oral cavity/pharynx (*N* = 85), small intestine (*N* = 70), other gastrointestinal tract (*N* = 33), other respiratory tract (*N* = 49), bone and cartilage (*N* = 77), male breast (*N* = 32), other female genital tract (*N* = 88), other male genital tract (*N* = 25), eye and orbit (*N* = 39), other urinary tract (*N* = 21), other endocrine glands (*N* = 26), and unknown primary site (*N* = 660).