Cancer risk in older people living with human immunodeficiency virus infection in the United States

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Key points:

Cancer risk in 183,542 older people living with HIV infection (PLWH) was evaluated using data from the HIV/AIDS Cancer Match Study. Relative risk of most cancers decreased with age, but absolute risks were higher for some cancers.

Running title: Cancer risk in older HIV-infected people

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ABSTRACT

Background: Cancer risk is increased in people living with HIV (PLWH). Improved survival has led to an aging of PLWH. We evaluated the cancer risk in older PLWH (age ≥50 years).

Methods: We included data from the HIV/AIDS Cancer Match Study (1996-2012) and evaluated risk of Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, and cervical, anal, lung, liver, oral cavity/pharyngeal, breast, prostate, and colon cancers in older PLWH compared to the general population by calculating the standardized incidence ratios (SIRs) and excess absolute risks (EARs). Cancer risk by time since HIV diagnosis was estimated using Poisson regression.

Results: We identified 10,371 cancers among 183,542 older PLWH. Risk was significantly increased for KS (SIR=103.34), NHL (SIR=3.05), Hodgkin lymphoma (SIR=7.61), and cervical (SIR=2.02), anal (SIR=14.00), lung (SIR=1.71), liver (SIR=2.91), and oral cavity/pharyngeal (SIR=1.66) cancers, and reduced for breast (SIR=0.61), prostate (SIR=0.47), and colon (SIR=0.63) cancers. SIRs declined with age for all cancers; however, EARs increased with age for anal, lung, liver, and oral cavity/pharyngeal cancers. Cancer risk was highest for most cancers within 5 years after HIV diagnosis; risk decreased with increasing time since HIV diagnosis for KS, NHL, lung cancer, and Hodgkin lymphoma.

Conclusions: Cancer risk is elevated among older PLWH. Although SIRs decrease with age, EARs are higher for some cancers, reflecting a greater absolute excess in cancer incidence among older PLWH. High risk in the first 5 years after HIV diagnosis for some cancers highlights the need for early HIV diagnosis and rapid treatment initiation.

Key words: HIV, cancer, aging, epidemiology

INTRODUCTION

People living with human immunodeficiency virus (HIV) infection (PLWH) have an increased cancer risk due to HIV-induced immunosuppression, co-infections with oncogenic viruses, and high prevalence of behavioral risk factors for cancer such as smoking [1-10]. Besides the AIDS-defining cancers (ADCs), i.e. Kaposi sarcoma (KS), certain non-Hodgkin lymphomas (NHLs), and cervical cancer, the risks of some non-AIDS defining cancers (NADCs), including lung, liver, anal, and oral cavity/pharyngeal cancers, and Hodgkin lymphoma are also increased [2, 5-10].

The introduction of highly active antiretroviral therapy (HAART) has led to a steady increase in the life expectancy of PLWH [11]. Consequently, the number of older PLWH in the US has also increased. In 2014, approximately 44% PLWH in the US were aged ≥50 years old, and 17% of new HIV diagnoses were made among ≥50 year-olds [12, 13]. Because of improved immunity due to HAART, rates of ADCs have declined over the past two decades [7, 14, 15]. However, rates of many NADCs increase with age. It is unclear whether age-related immune senescence in the setting of HIV-related immunosuppression will result in particularly elevated cancer rates among older PLWH.

PLWH aged ≥50 years are a heterogeneous group that includes long-term survivors who have lived with HIV infection for many years, and newly diagnosed individuals; whether cancer risk varies based on duration of HIV infection is uncertain. Prolonged immunosuppression in those with long-term HIV infection may increase cancer risk. Alternatively, people newly diagnosed with HIV infection at an older age may have more severe immunosuppression and a consequent high risk for cancer. People who are diagnosed with HIV at older ages may present late with a lower $CD4^+$ T-cell count, later HAART initiation, and more rapid progression to AIDS than young PLWH [16-19].

As the proportion of older PLWH continues to grow, a comprehensive evaluation of cancer risk in this population is needed. We therefore examined cancer risk in older PLWH compared to the general population, and evaluated the effects of age and time since HIV diagnosis on cancer risk.

SUBJECTS AND METHODS

Study population and outcomes

The U.S. HIV/AIDS Cancer Match (HACM) study links data from population-based HIV and cancer registries using a probabilistic algorithm (https://hivmatch.cancer.gov) [14]. This analysis included data from 9 U.S. states/territories (See Table 1 note). The HACM Study was approved by the institutional review boards at the National Cancer Institute and, as required, participating cancer and HIV registries.

The HIV diagnosis date was identified from HIV registries as the date of the first available positive serological test for HIV infection. The follow-up for each person started at the later of the start of cancer registry coverage, 4 months after the HIV report date (or AIDS diagnosis date if earlier), or age 50 years, and ended at the earlier of death or end of cancer registry coverage.

We evaluated risk of ADCs: KS, cervical cancer, and NHL (overall and by subtypes: diffuse large B cell lymphoma [DLBCL], Burkitt lymphoma, primary central nervous system [CNS] lymphoma, and other/unspecified NHLs); and certain NADCs which have increased incidence among PLWH: cancers of the anus, lung, liver, and oral cavity/pharynx, and Hodgkin lymphoma [5]. Female breast, colon, and prostate cancers were also included; though their rates increase with age, these cancers are not elevated among PLWH [5]. The remaining cancers were grouped together in a separate category. Cancers were classified by using the International Classification of Diseases for Oncology (3rd Edition) topography and morphology codes for invasive cancers (See Supplemental Table 1) [20].

Statistical analyses

We compared cancer incidence rates between PLWH and the general population by calculating standardized incidence ratios (SIRs), which measures relative risk, and excess absolute risks (EARs), which measures absolute risk. SIRs were calculated as observed divided by the expected number of cases; expected cases were estimated by applying general population cancer incidence rates to the HIV population by age, sex, race/ethnicity, calendar year, and cancer registry. Since the AIDS epidemic affected the contemporaneous rates of KS and primary CNS lymphoma in the general population, we calculated the expected number of cases for these cancers with pre-AIDS epidemic (1973-1979) general population cancer incidence rates obtained from the Surveillance, Epidemiology, and End Results (SEER) Program, stratified by race, sex, and age [21]. EARs for each cancer were estimated as the difference between the observed and expected cancer rates for age groups 50-59 and ≥60 years. For comparison, we also evaluated the SIRs and EARs among PLWH <50 years of age.

Among PLWH, we estimated cancer risk according to age (50-59, 60-69, ≥70 years), AIDS diagnosis (yes/no), and time since HIV diagnosis (≤5, 5.01-10, 10.01-15, and ≥15.01 years) by fitting Poisson regression models for each cancer type. Incidence rate ratios were adjusted (aIRRs) for race/ethnicity, sex/risk group, calendar year, region, and prior AIDS diagnosis and time since HIV diagnosis (in models for age) or age (in models for time since HIV diagnosis). Age, calendar year, prior AIDS diagnosis, and time since HIV diagnosis variables were updated over time.

We conducted some sensitivity analyses. Since outmigration of people from registry areas may result in over-estimating the person-time at risk, we decreased the person-time by 10% for PLWH after 10 years of follow-up and recalculated the SIRs [22]. It is possible that more cancer cases may be diagnosed shortly after HIV diagnosis because there may be a period of increased medical care around

the time of HIV diagnosis. Hence, we excluded the first year after HIV diagnosis date and re-estimated cancer risk according to time since HIV diagnosis. As risk of ADCs and NADCs have changed since the introduction of HAART, we restricted the follow-up time to calendar years 2001-2012 and recalculated the SIRs and aIRRs. Finally, we evaluated whether associations between age and cancer risk differed by time since HIV diagnosis, and associations between time since HIV diagnosis and cancer risk differed by age.

RESULTS

We studied 183,542 PLWH aged ≥50 years old who contributed 928,194 person-years of follow-up (Table 1). The person-time distribution was: 75.1% in 50-59-year-olds, 20.4% in 60-69-year-olds, and 4.5% in 70+-year-olds. A large fraction of person-time was contributed by non-Hispanic blacks (47.6%), men (74.3%), and those with a prior AIDS diagnosis (71.9%). A large proportion of person-time for the time since HIV diagnosis was unknown (22.2%). Among PLWH with a known date of HIV diagnosis, more than 60% were infected with HIV for at least 5 years and approximately 20% were living with HIV infection for more than 15 years.

During the follow-up, 10,371 cancers were diagnosed, of which 1,647 (15.9%) were ADCs and 8,724 (84.1%) were NADCs (Table 2). As expected, rates were increased in older PLWH compared to the general population for KS (SIR=103.34), total NHL (SIR=3.05), and cervical cancer (SIR=2.02). Among NHLs, rates were strongly elevated for CNS lymphoma (SIR=47.39) and Burkitt lymphoma (SIR=13.75). Among the NADCs, a very high risk of anal cancer (SIR=14.00) was observed followed by Hodgkin lymphoma (SIR=7.61). Rates were moderately increased for liver (SIR=2.91), lung (SIR=1.71), and oral

cavity/pharyngeal cancers (SIR=1.66). Furthermore, breast (SIR=0.61), prostate (SIR=0.47), and colon cancer rates (SIR=0.63) were significantly lower among PLWH than the general population. The SIRs did not differ appreciably after adjusting the person-time for late follow-up, or by restricting analyses to calendar years 2001-2012 (Supplementary Tables 2 and 4).

A comparison of SIRs and EARs by age for evaluated cancers is depicted in Figure 1. The SIRs were the highest for the youngest age group (<50 years) for all cancers and decreased with age, except for Hodgkin lymphoma, for which the SIRs were largely constant. The EARs also decreased with age for KS, NHL, cervical cancer, and Hodgkin lymphoma. In contrast, the EARs increased with age for cancers of the anus, lung, liver, and oral cavity/pharynx.

When cancer incidence rates were examined by age group among PLWH (Table 3), we observed a significant decrease in KS risk with increasing age. When compared to 50-59-year-olds, PLWH who were 60-69 (aIRR=0.68) or ≥70 years old (aIRR=0.43) had lower KS rates (p-trend=0.0014). In contrast, rates for lung, prostate, and colon cancers increased with age (p-trend<0.0001) while the trend for breast cancer was borderline significant (p-trend=0.0575). Liver and oral cavity/pharyngeal cancer rates were higher among 60-69-year-olds compared to the 50-59-year age group (p-trend<0.05). No association between age and cancer risk was observed for NHL (total or subtypes), cervical cancer, anal cancer, or Hodgkin lymphoma (p-trend>0.05).

PLWH with a prior AIDS diagnosis had increased KS, NHL (particularly, DLBCL [aIRR=1.97] and CNS lymphomas [aIRR=5.17]), anal, lung, and oral cavity/pharyngeal cancer, and Hodgkin lymphoma rates compared to those who were not previously diagnosed with AIDS (aIRRs ranging from 1.37 to 2.66, Table 3). Prostate cancer rates were lower among those with a prior AIDS diagnosis (aIRR=0.84), while cervical, liver, breast, and colon cancer rates were not significantly different with prior AIDS.

Risk of most cancers was highest within the first 5 years after HIV diagnosis, and gradually decreased over time (Table 4). Significant decreasing trends were observed for KS (p-trend<0.0001), total NHL (p-trend<0.0001), lung cancer (p-trend=0.0002), breast cancer (p-trend=0.02), and Hodgkin lymphoma (p-trend=0.04), while a marginally statistically significant trend was observed for prostate cancer (p-trend=0.07). In contrast, there was an indication that risk increased with increasing time since HIV diagnosis for anal (p-trend=0.07) and liver cancers (p-trend=0.08). Excluding the first year after HIV diagnosis did not affect our results (Supplementary Table 3). Restricting the analyses to calendar years 2001-2012 did not affect the associations between age or time since HIV diagnosis and cancer risk (Supplementary Tables 5 and 6).

The associations between age and cancer risk did not differ by time since HIV diagnosis for all cancers (all p-interaction>0.05). However, there was significant heterogeneity in the association between time since HIV diagnosis and cancer risk by age for NHL (p-interaction=0.0026) and Hodgkin lymphoma (p-interaction=0.0211). The ratios for NHL decreased with time since HIV diagnosis for both age categories (p-trend<0.0001 for ages 50-59 and ≥60 years). For Hodgkin lymphoma, the trend for decreasing rates with time since HIV diagnosis was only observed for ≥60-year-olds (p-trend=0.0063), but not among those who were 50-59 years old (p-trend=0.4065).

DISCUSSION

With the success of HAART, HIV infection has transformed from a terminal illness to a more manageable chronic disease. Consequently, more PLWH are reaching older ages. In our analyses that included more than 180,000 older PLWH, we observed that cancer risk was elevated in older PLWH compared to the general population, though the relative risk for most cancers declined with age. However, EARs, which measure absolute risk and thus reflect the number of excess cancers occurring

among PLWH, increased with age for some NADCs. We also observed that for many cancers, cancer risk was highest within the first five years after HIV diagnosis.

In the past 20 years, there has been a steady shift in the demographic profile of the HIV/AIDS epidemic in the U.S. towards the older age groups. In 2002, the CDC estimated that approximately 8.5% of the PLWH were over 50 years of age, and that number had increased to 44% in 2014 [12]. With aging, there is a complex interaction between various biological processes which may modulate cancer risk among PLWH: (i) factors related to aging, including age-related immune senescence; (ii) factors associated with HIV infection and its related immune dysfunction, such as HIV viral load, $CD4^+$ T-cell count, and effectiveness of HAART; and (iii) various host factors that may affect cancer risk, such as viral coinfections and smoking. Furthermore, the immunosuppressive state in PLWH changes over time. The natural course of HIV infection is characterized by progressive decline in immune function from primary HIV infection to symptomatic disease with onset of AIDS-defining conditions [23]. HAART alters the natural history of HIV infection with gradual improvement of immunosuppressive state and restoration of CD4+ T-cell count over time. In addition, the duration of immunosuppressed state of a person infected with HIV also increases with time.

Few previous studies could evaluate cancer risk in older PLWH as this population has historically been too small to target [24, 25]. In our study, we observed that the risk of ADCs and certain NADCs were elevated in older PLWH compared to the general population, as has been previously reported in mostly young PLWH [3, 7, 26]. Because cancer risk increases with age, and PLWH are at a high risk for cancer, the aging of PLWH raises the question of whether the combined effect of age and HIV infection will further increase cancer risk in PLWH. As captured by SIRs, we did not observe an amplified cancer risk among PLWH associated with aging. In fact, the SIRs were highest for the young PLWH and declined

with age, except for Hodgkin lymphoma, suggesting that HIV-related immunosuppression may play a larger role in cancer development in younger age groups.

Although the risk of anal, lung, liver, and oral cavity/pharyngeal cancers in PLWH relative to the general population decreased with age, there was an increase in the excess cancer rates in absolute terms, as reflected in the EARs. Due to increasing cancer incidence in the general population with age, even a modest decrease in SIRs with advancing age could lead to an increase in EARs and thus number of cancer cases. Thus, as PLWH continue to age, we may continue to observe an increase in the absolute number of these NADCs.

Risks for KS, NHLs, Hodgkin lymphoma, lung, and breast cancer were highest within the first 5 years after HIV diagnosis. The intensity of immunosuppression may be highest in the initial period, as newly diagnosed PLWH are untreated and may be especially immunosuppressed [27, 28]. Alternatively, it is possible that people who survived for several years with HIV infection may represent a healthy subset of PLWH, while those with newly acquired and diagnosed HIV may have a higher prevalence of cancer risk factors. For example, a diagnosis of HIV infection may lead to changes in lifestyle habits such as reducing cigarette smoking [29]. Increased medical surveillance shortly after HIV diagnosis may also increase the possibility of detecting cancers, but excluding the first year of follow-up after HIV diagnosis did not eliminate the trend that we observed. In contrast, anal and liver cancer rates marginally increased with time since HIV diagnosis, which may represent the role of prolonged immunosuppression in increasing cancer rates due to human papillomavirus or hepatitis virus co-infections.

We observed lower risk of breast, prostate, and colon cancer rates in older PLWH compared to the general population, as has been previously reported [26, 30-33]. As in the general population, prostate and colon cancer rates increased with age, and the trend for breast cancer was borderline

significant. As these are common screen-detectable cancers, it has been speculated that reduced rates of these cancers may reflect lower rates of cancer screening among PLWH compared with the general population. However, recent studies suggest that the deficit of breast, colon, and prostate cancers among PLWH cannot be completely explained by lower rates of cancer screening [34, 35]. Biological explanations for these deficits need to be explored further.

Given the aging of PLWH and the increase in the burden of NADCs, it is essential to target available cancer prevention and screening strategies towards this population. Cancer prevention among PLWH is largely based on restoring immunity with HAART and reducing traditional cancer risk factors [36]. Timely linkage of care with HAART initiation and uninterrupted treatment for people who have been newly diagnosed with HIV infection is essential to restore immunity. This also gives an opportunity for healthcare providers to diagnose and treat coinfections, and to initiate counseling on modification of lifestyle behaviors such as smoking. General population screening guidelines for breast, prostate, and colon cancers should be followed. Cervical cancer screening is recommended at more frequent intervals than for HIV-uninfected women [37, 38], and the benefits of anal cancer screening are still being evaluated [37, 38]. Finally, screening for lung cancers with low-dose computerized tomography may be beneficial, but more data are needed among PLWH [37, 38].

A strength of our study was the use of a large population-based cohort of more than 180,000 PLWH aged ≥50 years with systematic cancer ascertainment, and the evaluation of cancer risk by time since HIV diagnosis. However, we were unable to include information on HAART use, $CD4^+$ T-cell count, or HIV viral load in our analyses. Therefore, we cannot definitively interpret trends with respect to time since HIV diagnosis. In addition, our data do not include information about cancer risk factors, such as cigarette smoking and viral co-infection. Since the timing of acquiring HIV infection was not known, HIV duration could be calculated only from the first available positive serological test date, and 22.2% of

person-time contributed by PLWH in our study was missing this information. We were unable to adjust for competing risks due to coexisting comorbidities in our analyses. We used general population as our control group because we did not have access to an ideal HIV-uninfected population which may have similar characteristics to PLWH [39]. Finally, this analysis includes only PLWH who have been diagnosed with HIV, and an estimated 13% of PLWH are unaware that they are infected, more than 7% of whom may be over 50 years of age [40].

In conclusion, rates of several cancer types are elevated in older PLWH compared to the general population, albeit in the absence of information on important cancer risk factors. However, the relative risk of cancers is lower than for younger PLWH, suggesting that the combined effect of aging and HIV does not further amplify the relative risk of cancers. Despite lower relative risks, the absolute risk difference is higher for some NADCs among older PLWH leading to a greater incidence of excess cancers in this group. Thus, there is a continued need for cancer prevention and early detection among older PLWH. Cancer risk was also highest within the first 5 years after HIV diagnosis for most cancers, underscoring the importance of early HIV diagnosis, rapid initiation of HAART after HIV diagnosis, and interventions to reduce traditional risk factors in older PLWH.

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DISCLAIMER:

The views expressed in this paper 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.

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POTENTIAL CONFLICTS OF INTEREST:

All authors: No reported conflicts of interest.

REFERENCES

1. Park LS, Hernandez-Ramirez RU, Silverberg MJ, Crothers K, Dubrow R. Prevalence of non-HIV cancer risk factors in persons living with HIV/AIDS: a meta-analysis. Aids **2016**; 30(2): 273-91.
2. Althoff KN, McGinnis KA, Wyatt CM, et al. Comparison of risk and age at diagnosis of myocardial infarction, end-stage renal disease, and non-AIDS-defining cancer in HIV-infected versus uninfected adults. Clin Infect Dis **2015**; 60(4): 627-38.
3. Clifford GM, Polesel J, Rickenbach M, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J Natl Cancer Inst **2005**; 97(6): 425-32.
4. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet **2007**; 370(9581): 59-67.
5. 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**.
6. Massad LS, Hessol NA, Darragh TM, et al. Cervical cancer incidence after up to 20 years of observation among women with HIV. Int J Cancer **2017**; 141(8): 1561-5.
7. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. Ann Intern Med **2008**; 148(10): 728-36.
8. Robbins HA, Pfeiffer RM, Shiels MS, Li J, Hall HI, Engels EA. Excess cancers among HIV-infected people in the United States. J Natl Cancer Inst **2015**; 107(4).
9. Shiels MS, Cole SR, Kirk GD, Poole C. A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. J Acquir Immune Defic Syndr **2009**; 52(5): 611-22.
10. Shiels MS, Pfeiffer RM, Gail MH, et al. Cancer burden in the HIV-infected population in the United States. J Natl Cancer Inst **2011**; 103(9): 753-62.

11. Samji H, Cescon A, Hogg RS, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. PLoS One **2013**; 8(12): e81355.

12. Centers for Disease Control and Prevention: Diagnoses of HIV infection among adults aged 50 years and older in the United States and dependent areas, 2010-2014. HIV Surveillance Supplemental Report 2016 21(2): 1-69.

13. Centers for Disease Control and Prevention: Diagnoses of HIV Infection in the United States and Dependent Areas, 2014. HIV Surveillance Report 2014 26: 1-123.

14. Biggar RJ, Chaturvedi AK, Goedert JJ, Engels EA. AIDS-related cancer and severity of immunosuppression in persons with AIDS. J Natl Cancer Inst **2007**; 99(12): 962-72.

15. Engels EA, Pfeiffer RM, Goedert JJ, et al. Trends in cancer risk among people with AIDS in the United States 1980-2002. Aids **2006**; 20(12): 1645-54.

16. Smith RD, Delpech VC, Brown AE, Rice BD. HIV transmission and high rates of late diagnoses among adults aged 50 years and over. Aids **2010**; 24(13): 2109-15.

17. Althoff KN, Gebo KA, Gange SJ, et al. CD4 count at presentation for HIV care in the United States and Canada: are those over 50 years more likely to have a delayed presentation? AIDS Res Ther **2010**; 7: 45.

18. Brooks JT, Buchacz K, Gebo KA, Mermin J. HIV infection and older Americans: the public health perspective. Am J Public Health **2012**; 102(8): 1516-26.

19. He L, Pan X, Dou Z, et al. The Factors Related to CD4+ T-Cell Recovery and Viral Suppression in Patients Who Have Low CD4+ T Cell Counts at the Initiation of HAART: A Retrospective Study of the National HIV Treatment Sub-Database of Zhejiang Province, China, 2014. PLoS One **2016**; 11(2): e0148915.

20. Fritz A, Percy C, Jack A, et al. International Classification of Diseases for Oncology, Third Edition, First Revision. Geneva: World Health Organization, **2013**.

21. Chaturvedi AK, Mbulaiteye SM, Engels EA. Underestimation of relative risks by standardized incidence ratios for AIDS-related cancers. Ann Epidemiol **2008**; 18(3): 230-4.

22. Simard EP, Pfeiffer RM, Engels EA. Spectrum of cancer risk late after AIDS onset in the United States. Arch Intern Med **2010**; 170(15): 1337-45.

23. Mindel A, Tenant-Flowers M. ABC of AIDS: Natural history and management of early HIV infection. Bmj **2001**; 322(7297): 1290-3.

24. Biggar RJ, Kirby KA, Atkinson J, McNeel TS, Engels E. Cancer risk in elderly persons with HIV/AIDS. J Acquir Immune Defic Syndr **2004**; 36(3): 861-8.

25. Yanik EL, Katki HA, Engels EA. Cancer risk among the HIV-infected elderly in the United States. Aids **2016**; 30(10): 1663-8.

26. Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. Int J Cancer **2008**; 123(1): 187-94.

27. Rosenberg ES, Billingsley JM, Caliendo AM, et al. Vigorous HIV-1-specific CD4+ T cell responses associated with control of viremia. Science **1997**; 278(5342): 1447-50.

28. Fleury S, Rizzardi GP, Chapuis A, et al. Long-term kinetics of T cell production in HIV-infected subjects treated with highly active antiretroviral therapy. Proc Natl Acad Sci U S A **2000**; 97(10): 5393-8.

29. Wang Y, Chen X, Li X, et al. Cigarette smoking among Chinese PLWHA: An exploration of changes in smoking after being tested HIV positive. AIDS Care **2016**; 28(3): 365-9.

30. Herida M, Mary-Krause M, Kaphan R, et al. Incidence of non-AIDS-defining cancers before and during the highly active antiretroviral therapy era in a cohort of human immunodeficiency virus-infected patients. J Clin Oncol **2003**; 21(18): 3447-53.

31. Pantanowitz L, Dezube BJ. Reasons for a deficit of breast cancer among HIV-infected patients. J Clin Oncol **2004**; 22(7): 1347-8; author reply 9-50.

32. Frisch M, Biggar RJ, Engels EA, Goedert JJ. Association of cancer with AIDS-related immunosuppression in adults. Jama **2001**; 285(13): 1736-45.

33. Shiels MS, Goedert JJ, Moore RD, Platz EA, Engels EA. Reduced risk of prostate cancer in U.S. Men with AIDS. Cancer Epidemiol Biomarkers Prev **2010**; 19(11): 2910-5.

34. Marcus JL, Chao CR, Leyden WA, et al. Prostate cancer incidence and prostate-specific antigen testing among HIV-positive and HIV-negative men. J Acquir Immune Defic Syndr **2014**; 66(5): 495-502.

35. Coghill AE, Engels EA, Schymura M, Mahale P, Shiels MS. Lower Risks of Breast, Prostate, and Colorectal Cancers among HIV-infected Individuals in the United States. J Natl Cancer Inst **2017**.

36. Dubrow R, Silverberg MJ, Park LS, Crothers K, Justice AC. HIV infection, aging, and immune function: implications for cancer risk and prevention. Curr Opin Oncol **2012**; 24(5): 506-16.

37. Gopal S, Achenbach CJ, Yanik EL, Dittmer DP, Eron JJ, Engels EA. Moving forward in HIV-associated cancer. J Clin Oncol **2014**; 32(9): 876-80.

38. Goncalves PH, Montezuma-Rusca JM, Yarchoan R, Uldrick TS. Cancer prevention in HIV-infected populations. Semin Oncol **2016**; 43(1): 173-88.

39. Wong C, Althoff K, Gange SJ. Identifying the appropriate comparison group for HIV-infected individuals. Curr Opin HIV AIDS **2014**; 9(4): 379-85.

40. 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, 2014. HIV Surveillance Supplemental Report 21(4).

TABLES

Table 1: Person-years contributed by older people living with HIV infection according to age categories.

Characteristics	% of total Person-years			
	Total (928,124 person-years)	Age 50 – 59 years (697,455 person-years)	Age 60 – 69 years (189,015 person-years)	Age ≥ 70 years (41,724 person-years)
Race/ethnicity				
Non-Hispanic White	25.8	25.8	26.1	25.6
Non-Hispanic Black	47.6	48.0	46.5	45.3
Hispanic	26.6	26.2	27.3	29.0
Sex/risk group				
MSM	27.0	27.0	27.1	25.9
Male IDU	22.1	23.3	19.9	11.5
MSM/IDU	3.9	4.4	2.8	1.2
Male other/unknown	21.3	19.4	25.4	34.6
Female IDU	7.5	8.5	5.1	2.3
Female other/unknown	18.2	17.4	19.7	24.6
Calendar year				
1996 - 2000	2.9	3.1	2.3	2.3
2001 - 2005	23.3	24.4	20.0	19.6
2006 - 2012	73.8	72.5	77.7	78.2
Prior AIDS diagnosis				
No	28.1	28.5	26.9	26.1
Yes	71.9	71.5	73.1	73.9
Time since HIV diagnosis, years				
Unknown	22.2	22.0	22.5	22.7
≤5	16.9	17.0	16.2	16.1
5.01 - 10	24.0	24.0	23.6	24.6
10.01 - 15	20.9	20.9	20.7	21.0
≥15.01	16.1	16.0	16.9	15.5

Abbreviations: IDU, injection drug users; MSM, men who have sex with men

Note: Participating registries with years of coverage: Colorado (covering 1996-2007), Connecticut (2005-2010), Georgia (2004-2012), Maryland (2008-2012), Michigan (1996-2010), New Jersey (1996-2012), New York (2001-2012), Puerto Rico (2003-2012), and Texas (1999-2009).

Table 2: Risk of cancers in older people living with HIV infection (age ≥ 50 years)

Cancers	Observed no. of cases	Expected no. of cases	IR per 100,000 PY	SIR	95% CI
All cancers	10,371	8,929	1,117.3	1.16	1.14 - 1.18
AIDS-defining cancers					
Kaposi sarcoma	338	3.3	36.4	103.34	92.62 - 114.97
Non-Hodgkin lymphoma	1,222	401.2	131.7	3.05	2.88 - 3.22
Diffuse large B cell	674	110.0	72.6	6.12	5.67 - 6.61
Burkitt	103	7.5	11.1	13.75	11.23 - 16.68
CNS	74	8.1	8.0	47.39	37.21 - 59.49
Other/Unspecified	371	282.1	39.9	1.32	1.18 - 1.46
Cervical cancer	87	43.0	36.5	2.02	1.62 - 2.49
Non-AIDS defining cancers					
Anus	524	37.4	56.5	14.00	12.82 - 15.25
Lung	1,725	1,012	185.8	1.71	1.63 - 1.79
Liver	805	276.4	86.7	2.91	2.71 - 3.12
Hodgkin lymphoma	253	33.3	27.3	7.61	6.70 - 8.60
Oral cavity/pharynx	461	278.4	49.7	1.66	1.51 - 1.81
Female breast	329	542.0	137.9	0.61	0.54 - 0.68
Prostate	1,341	2,829	194.5	0.47	0.45 - 0.50
Colon (excluding rectum)	360	571.3	38.8	0.63	0.57 - 0.70
Other cancers	2,926	5,731	315.2	1.01	0.97 - 1.05

Abbreviations: CI, confidence intervals; CNS, central nervous system; IR, incidence rate; PY, person-years; SIR, standardized incidence ratio

Table 3: Risk of cancers in older people living with HIV infection according to age and prior AIDS diagnosis

Cancers	Age 50-59 years		Age 60-69 years		Age ≥70 years		p- trend	AIDS diagnosis (Yes vs. No)
	N	aIRR[a] (95% CI)	N	aIRR[a] (95% CI)	N	aIRR[a] (95% CI)		aIRR[b] (95% CI)
AIDS-defining cancers								
Kaposi sarcoma	280	Reference	51	0.68 (0.51 - 0.92)	7	0.43 (0.20 - 0.92)	0.0014	1.86 (1.40 - 2.47)
Non-Hodgkin lymphoma	946	Reference	227	0.90 (0.78 - 1.04)	49	0.88 (0.66 - 1.18)	0.1259	1.74 (1.50 - 2.01)
Diffuse large B cell	521	Reference	127	0.90 (0.74 - 1.10)	26	0.84 (0.56 - 1.25)	0.2073	1.97 (1.61 - 2.41)
Burkitt[c]	82	Reference	21	0.80 (0.49 - 1.30)	-	-	0.3690	1.22 (0.77 - 1.92)
CNS[c]	63	Reference	11	0.53 (0.28 - 1.01)	-	-	0.0533	5.17 (2.25 - 12.21)
Other/Unspecified	280	Reference	71	0.94 (0.73 - 1.21)	20	1.12 (0.71 - 1.77)	0.3331	1.50 (1.18 - 1.90)
Cervical cancer[c]	66	Reference	21	1.10 (0.67 - 1.82)	-	-	0.6957	1.50 (0.91 - 2.49)
Non-AIDS defining cancers								
Anus	397	Reference	112	1.05 (0.85 - 1.29)	15	0.66 (0.40 - 1.11)	0.4494	2.66 (2.04 - 3.47)
Lung	1,030	Reference	552	2.11 (1.90 - 2.34)	143	2.62 (2.20 - 3.13)	< 0.0001	1.37 (1.22 - 1.53)
Liver	546	Reference	226	1.61 (1.38 - 1.89)	33	1.29 (0.91 - 1.84)	< 0.0001	0.92 (0.78 - 1.09)
Hodgkin lymphoma	193	Reference	53	1.00 (0.74 - 1.36)	7	0.58 (0.27 - 1.23)	0.3244	2.19 (1.55 - 3.09)
Oral cavity/pharynx	315	Reference	132	1.55 (1.26 - 1.90)	14	0.76 (0.44 - 1.30)	0.0310	1.67 (1.31 - 2.12)
Female breast	232	Reference	77	1.26 (0.97 - 1.63)	20	1.32 (0.83 - 2.09)	0.0575	1.03 (0.82 - 1.31)
Prostate	627	Reference	550	3.11 (2.77 - 3.49)	164	4.12 (3.46 - 4.90)	< 0.0001	0.84 (0.74 - 0.94)
Colon (excluding rectum)	177	Reference	125	2.59 (2.06 - 3.26)	58	5.28 (3.90 - 7.15)	< 0.0001	0.89 (0.71 - 1.13)
Other cancers	1,845	Reference	829	1.69 (1.55 - 1.83)	252	2.34 (2.05 - 2.68)	< 0.0001	1.25 (1.15 - 1.36)

Abbreviations: aIRR, adjusted incidence rate ratio; CI, confidence intervals; CNS, central nervous system

[a] Adjusted for race, sex/risk group, calendar year, region, prior AIDS diagnosis, and time since HIV diagnosis

[b] Adjusted for age, race, sex/risk group, calendar year, region, and time since HIV diagnosis

[c] Adjusted risk estimates and p-trend for these cancers are presented for age groups 50-59 years and ≥60 years because the number of cancers that occurred in ≥ 70-years category were too few (Burkitt lymphoma, n=1; CNS lymphoma, n=2; cervical cancer; n=2)

Table 4: Risk of cancers in older HIV-infected individuals according to the time since HIV diagnosis

Cancers	≤5 years		5.01-10 years		10.01-15 years		≥15.01 years		p-trend
	N	aIRR[a] (95% CI)	N	aIRR[a] (95% CI)	N	aIRR[a] (95% CI)	N	aIRR[a] (95% CI)	
AIDS-defining cancers									
Kaposi sarcoma	95	Reference	81	0.58 (0.43 - 0.79)	55	0.44 (0.31 - 0.63)	40	0.43 (0.29 - 0.65)	< 0.0001
Non-Hodgkin lymphoma	355	Reference	308	0.60 (0.51 - 0.70)	204	0.45 (0.38 - 0.54)	123	0.36 (0.29 - 0.45)	< 0.0001
Diffuse large B cell	183	Reference	164	0.60 (0.49 - 0.75)	122	0.50 (0.39 - 0.64)	66	0.36 (0.26 - 0.49)	< 0.0001
Burkitt	33	Reference	22	0.44 (0.25 - 0.76)	18	0.39 (0.21 - 0.72)	9	0.24 (0.11 - 0.53)	0.0001
CNS	24	Reference	19	0.54 (0.29 - 1.00)	10	0.33 (0.15 - 0.71)	10	0.46 (0.20 - 1.05)	0.0164
Other/Unspecified	115	Reference	103	0.63 (0.48 - 0.82)	54	0.39 (0.28 - 0.54)	38	0.38 (0.26 - 0.55)	< 0.0001
Cervical cancer	21	Reference	22	0.75 (0.40 - 1.37)	16	0.61 (0.31 - 1.23)	12	0.64 (0.29 - 1.43)	0.2004
Non-AIDS defining cancers									
Anus	59	Reference	99	1.03 (0.74 - 1.43)	140	1.50 (1.09 - 2.06)	95	1.21 (0.86 - 1.72)	0.0683
Lung	355	Reference	459	0.92 (0.80 - 1.06)	367	0.87 (0.74 - 1.02)	213	0.70 (0.58 - 0.84)	0.0002
Liver	98	Reference	155	0.97 (0.75 - 1.26)	180	1.17 (0.90 - 1.51)	157	1.20 (0.91 - 1.59)	0.0775
Hodgkin lymphoma	64	Reference	61	0.69 (0.48 - 0.99)	41	0.54 (0.36 - 0.82)	39	0.70 (0.45 - 1.09)	0.0405
Oral cavity/pharynx	79	Reference	117	1.02 (0.76 - 1.36)	96	0.93 (0.68 - 1.27)	66	0.82 (0.57 - 1.17)	0.2216
Female breast	75	Reference	90	0.85 (0.62 - 1.17)	63	0.72 (0.50 - 1.02)	38	0.64 (0.42 - 0.98)	0.0214
Prostate	231	Reference	363	1.08 (0.91 - 1.27)	272	0.94 (0.78 - 1.13)	191	0.86 (0.70 - 1.07)	0.0726
Colon (excluding rectum)	68	Reference	90	0.94 (0.68 - 1.30)	82	1.03 (0.73 - 1.45)	43	0.75 (0.49 - 1.14)	0.3239
Other cancers	568	Reference	741	0.91 (0.82 - 1.02)	643	0.91 (0.80 - 1.02)	429	0.79 (0.69 - 0.91)	0.0004

Abbreviations: CI, confidence intervals; IRR, incidence rate ratio

[a] Adjusted for age, race, sex/risk group, calendar year, region, and prior AIDS diagnosis

FIGURE

Figure 1: Risk of cancers in people living with HIV compared to the general population

Figure 1 legend: The figure plots the standardized incidence ratios (SIRs) on the left y-axis, the excess absolute risks (EARs) per 100,000 population on the right y-axis, and 3 age groups on the x-axis (< 50 years, 50-59 years, ≥60 years). Risks of 3 AIDS-defining cancers, i.e. Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer, are plotted in panels A, B, and C, respectively, and risks of 5 non-AIDS-defining cancers, i.e. anal cancer, lung cancer, liver cancer, Hodgkin lymphoma, and oral cavity/pharynx cancer, are plotted in panels D, E, F, G, and H, respectively.

Abbreviations: EAR, excess absolute risk; SIR, standardized incidence ratio

Figure 1.