Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2011 December ; 20(12): 2551–2559. doi: 10.1158/1055-9965.EPI-11-0777.

HIV infection, Immunodeficiency, Viral Replication and the Risk of Cancer

Michael J. Silverberg[1], **Chun Chao**[2], **Wendy A. Leyden**[1], **Lanfang Xu**[2], **Michael A. Horberg**[3], **Daniel Klein**[4], **William J. Towner**[5], **Robert Dubrow**[6], **Charles P. Quesenberry Jr**[1], **Romain S. Neugebauer**[1], and **Donald I. Abrams**[7,8]

[1]Kaiser Permanente Northern California, Oakland, CA, USA

[2]Kaiser Permanente Southern California, Pasadena, CA, USA

[3]Mid-Atlantic Permanente Research Institute, Rockville, MD, USA

[4]Kaiser Permanente Northern California, Hayward, CA, USA

[5]Kaiser Permanente Southern California, Los Angeles, CA, USA

[6]Yale School of Public Health and School of Medicine, New Haven, CT, USA

[7]San Francisco General Hospital, San Francisco, CA, USA

[8]University of California San Francisco, San Francisco, CA, USA

Abstract

Background—Few studies have compared cancer risk between HIV-infected individuals and a demographically-similar HIV-uninfected internal comparison group, adjusting for cancer risk factors.

Methods—We followed 20,775 HIV-infected and 215,158 HIV-uninfected individuals enrolled in Kaiser Permanente (KP) California for incident cancer from 1996–2008. Rate ratios (RR) were obtained from Poisson models comparing HIV-infected (overall and stratified by recent CD4 count and HIV RNA) with HIV-uninfected individuals, adjusted for age, sex, race/ethnicity, calendar period, KP region, smoking, alcohol/drug abuse, and overweight/obesity.

Results—We observed elevated RRs for Kaposi sarcoma (KS) (RR=199; P<0.001), non-Hodgkin lymphoma (NHL) (RR=15; P<0.001), anal cancer (RR=55; P<0.001), Hodgkin lymphoma (HL) (RR=19; P<0.001), melanoma (RR=1.8; P=0.001), and liver cancer (RR=1.8; P=0.013), a reduced RR for prostate cancer (RR=0.8; P=0.012), and no increased risk for oral cavity/pharynx (RR=1.4; P=0.14), lung (RR=1.2; P=0.15), or colorectal (RR=0.9; P=0.34) cancers. Lung and oral cavity/pharynx cancers were elevated for HIV-infected subjects in models adjusted only for demographics. KS, NHL, anal cancer, HL, and colorectal cancer had significant (P<0.05) trends for increasing RRs with decreasing recent CD4. The RRs for lung and oral cavity/pharynx cancer were significantly elevated with CD4 <200 cells/μL and for melanoma and liver cancer with CD4 <500 cells/μL. Only KS and NHL were associated with HIV RNA.

Conclusion—Immunodeficiency was positively associated with all cancers examined except prostate cancer among HIV-infected compared with HIV-uninfected individuals, after adjustment for several cancer risk factors.

Corresponding author: Michael J. Silverberg, PhD, MPH, Research Scientist, Kaiser Permanente Northern California, Division of Research, 2000 Broadway, Oakland, CA 94612, Michael.J.Silverberg@kp.org, Phone: 510-891-3801; fax: 510-891-3508.

Conflicts of interest: The authors report research grant support from Pfizer (MJS, CC, WAL, LX, MAH, DK, WJT, CPQ), Merck (MJS, CC, MAH, WJT, CPQ), Gilead (WJT) and Tibotec (WJT). No other conflicts are reported.

Impact—Earlier antiretroviral therapy initiation to maintain high CD4 levels might reduce the burden of cancer in this population.

Keywords

HIV/AIDS; cancer; immunodeficiency; viral replication; epidemiology

INTRODUCTION

Cancer remains a major cause of morbidity and mortality for HIV-infected individuals during the antiretroviral therapy (ART) era. The high risk of cancer in HIV-infected individuals compared with the general population (1–5) may be due in part to the higher prevalence in this population of traditional cancer risk factors, such as smoking (6–8), alcohol use (7, 9), and oncogenic virus coinfection (10–13). However there is increasing evidence that the elevated non-AIDS-defining cancer (NADC) risk may also be a direct consequence of HIV-induced immunodeficiency or inflammation (14–16).

With a few exceptions (17–18), most studies evaluating cancer risk in HIV-infected individuals have not included a demographically-similar HIV-uninfected internal comparison group, but rather have relied on general population external comparison groups, calculating standardized incidence ratios. Such an approach is susceptible to selection bias and does not allow for individual-level adjustment for important potential confounders such as smoking. Several recent studies have indicated that recent low CD4 counts may be associated with a higher risk of certain cancers, particularly virus-related cancers, although none of these studies included an HIV-uninfected comparison group, and adjustment for potential confounders was limited (14–16).

We previously reported on the incidence rate of NADC in HIV-infected versus demographically-similar HIV-uninfected subjects from the same healthcare system. After adjustment for demographic variables, the incidence rate for infection-related NADC as a group was markedly elevated for HIV-infected individuals and the incidence rate for infection-unrelated NADC as a group was modestly elevated (5). Here, we extend that work for several of the more common cancers with adjustment for several traditional cancer risk factors including smoking, alcohol/drug abuse, and overweight/obesity. We also evaluate the effect of HIV-specific factors on cancer risk, including time-dependent measures of CD4 count and HIV RNA level.

MATERIALS AND METHODS

Study design, setting and participants

We conducted a cohort study from 1996 to 2008 of adult HIV-infected and matched HIV-uninfected individuals within Kaiser Permanente (KP) Northern and Southern California (KPNC and KPSC, respectively), large integrated health care delivery systems providing comprehensive medical services to more than six million health plan members, representing roughly 30% of insured Californians (19). The health plans have maintained HIV registries including all known cases since 1980 in KPNC and 2000 in KPSC. The institutional review board at each institution approved the study, providing waivers of informed consent.

The index date for HIV-infected individuals was assigned as the earliest date after 1/1/96 (1/1/00 for KPSC) when a member met all of the following criteria: ≥18 years of age, known to be HIV-infected, and in HIV care, defined as the first recorded CD4 cell count measurement in the health system. Health plan members without HIV infection were then frequency-matched 10:1 by year of start of follow-up, age at start of follow-up (5-year age

groups), sex, and medical center. Subjects were followed from first health plan enrollment after 1/1/96 until the earliest of a cancer diagnosis, lost to follow-up, death or 12/31/08.

Data Sources

The HIV Registries include health plan members with documented HIV/AIDS, confirmed by medical chart review and comparisons of case lists with HIV clinics. Data elements maintained in the HIV registries include sex, race/ethnicity, HIV exposure risk (e.g., men who have sex with men, injection drug use), dates of HIV and AIDS diagnoses and date of death.

We identified all incident invasive cancers among HIV-infected and uninfected individuals by linkage with the KPNC and KPSC cancer registries, which are contributing sites to the Surveillance, Epidemiology, and End Results (SEER) Program. We had sufficient events among HIV-infected individuals to analyze the following 10 cancer types: Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), anal cancer, oral cavity and pharynx cancer, Hodgkin lymphoma (HL), liver cancer, lung cancer, melanoma, prostate cancer, and colorectal cancer.

Other data were obtained from the electronic medical record, including information on laboratory tests (CD4 and HIV RNA levels), demographics (age, sex, race/ethnicity, health plan enrollment), and clinical diagnoses/encounters, including alcohol or other drug abuse or dependence diagnoses (International Classification of Disease codes, version 9 [ICD-9]: 291, 292, 303–305.0, 305.2–305.5), overweight or obesity diagnoses (ICD-9: 278, 259.9, V85; internal weight/height codes), and tobacco use (305.1, V15, V65, 649, internal social history codes). For smoking, alcohol/drug abuse and overweight/obesity diagnoses, the potential risk factor was considered present if documented in the medical record, and not present otherwise. Thus, there was no missing information for these variables in the analysis. This was the best way to classify these factors in our data, since the lack of such diagnoses was not routinely recorded. In KPSC, hepatitis B virus (HBV) infection was defined by a positive HBV surface antigen test or detectable virus by PCR, and hepatitis C virus (HCV) infection was defined by a positive HCV antibody or HCV RNA test. In KPNC, both HBV and HCV infection were defined by inclusion in the Viral Hepatitis Registry. Individuals not tested for HBV or HCV were classified as not known to be infected.

Statistical Analysis

Although smoking, overweight/obese, and alcohol/drug abuse were ascertained at anytime during follow-up, they were treated as fixed variables in the analysis. Other variables fixed at baseline included sex, race/ethnicity (white, black/African-American, Hispanic, other/unknown), and KP region (KPNC/KPSC). To categorize the time-dependent variables recent CD4 and HIV RNA levels, follow-up for HIV-infected individuals was divided into 6-month intervals. The most recent CD4 (≤200, 201–499, ≥500 cells/μL) and HIV RNA (≥10,000, 501–9,999, ≤500 copies/mL) test results prior to the start of an interval were then assigned to that interval. Other time-dependent variables updated throughout follow-up including age (<40, 40–49, 50–64, 65+ years) and calendar period (1996–1998, 1999–2001, 2002–2004, 2005–2008).

We first computed cancer incidence rates per 100,000 person-years by HIV status. Adjusted rate ratios (RR) for HIV status were then obtained from a demographic-adjusted Poisson regression model included terms for HIV status, age, sex, race/ethnicity, calendar period, and KP region. We also obtained RRs from a fully-adjusted model with additional terms for smoking, overweight/obesity, and alcohol/drug abuse. Next, we compared the risk of cancer

in HIV-infected individuals stratified by recent CD4 count with the risk among HIV-uninfected individuals (reference group). This approach allows for a direct evaluation of whether cancer risk in HIV patients with a more intact immune system has approached the cancer risk in the general population. An increasing trend of the RR for HIV infection status with lower CD4 counts among HIV-infected individuals was assessed by the likelihood ratio test. An analogous analysis was then performed that compared the risk of cancer in HIV-infected individuals stratified by recent HIV RNA level with the risk among HIV-uninfected individuals.

Finally, for HIV-infected individuals only, we computed adjusted RRs for recent CD4 count and recent HIV RNA in the same multivariable Poisson model. Other terms included in the model included age, sex, race/ethnicity, calendar period, KP region, smoking, overweight, alcohol/drug abuse, prior ART use, HIV exposure risk, and years known HIV-infected.

All analyses were performed with SAS (Version 9.1, Cary, North Carolina, USA), using proc GENMOD for Poisson regression.

RESULTS

We identified 20,775 HIV-infected individuals contributing 90,961 person-years and 215,158 HIV-uninfected individuals contributing 1,133,444 person-years. Baseline characteristics are presented in Table 1. Most study subjects were male. HIV-infected individuals compared with HIV-uninfected individuals were more likely to be White or African-American (among those with known race/ethnicity), to have a recorded history of smoking, alcohol abuse, other drug abuse, HBV and HCV infection, and somewhat less likely to have a diagnosis of overweight/obesity.

Demographic-adjusted RRs for HIV-infected individuals compared with HIV-uninfected individuals are presented in Table 2. The RR was elevated for each cancer type except for prostate cancer (significantly reduced RR) and colorectal cancer (RR not significantly different than 1.0). The demographic- and fully-adjusted RR for each cancer type was similar, except for lung, oral cavity/pharynx, and liver cancers. The demographic-adjusted RRs for lung and oral cavity/pharynx cancers were significantly elevated, whereas the fully adjusted RRs were not. For liver cancer, full adjustment reduced the RR from 2.6 to 1.8; however the fully-adjusted RR remained significant. In sensitivity analyses, additional models for lung and oral cavity/pharynx cancers were considered that adjusted for demographic variables plus each of the three risk factors separately (i.e., smoking, alcohol/drug abuse, or overweight/obesity). Although adjustment for demographic variables plus smoking attenuated the RRs slightly more than did adjustment for demographic variables plus each of the other risk factors, none of the separately adjusted models completely eliminated the statistically significant effect of HIV infection status (data not shown), as observed for the fully-adjusted models for these cancers.

As shown in Table 3, we observed a trend of higher RRs with lower recent CD4 levels among HIV-infected individuals compared with the risk in HIV-uninfected individuals for the following cancers types: KS ($P<0.001$), NHL ($P<0.001$), HL ($P<0.001$), anal ($P=0.005$) and colorectal cancers ($P=0.028$). These same cancers, with the exception of colorectal cancer, had an elevated RR for HIV-infected individuals with CD4 count levels ≥500 cells/μL (although the RR was substantially lower than for lower CD4 count levels). Specifically, for the two NADCs, anal cancer and HL, the RRs for CD4 ≥500 cells/μL were 33.8 (95% CI=17.8–64.3) and 13.5 (95% CI=7.2–25.1), respectively, and for CD4 <200 cells/μL, the RRs were 91.5 (95% CI=48.0–174.5) and 55.3 (95% CI=31.3–97.9), respectively. Lung, colorectal and oral cavity/pharynx cancer RRs were only elevated for HIV-infected

individuals with CD4<200 cells/μL, with RRs of 2.2 (95% CI=1.3–3.6), 1.8 (95% CI=1.0–3.3), and 2.5 (95% CI=1.2–5.4), respectively. Melanoma and liver cancer RRs were elevated for CD4 counts<200 and 201–499 cells/mL, but not for ≥500 cells/μL. The prostate cancer RR was significantly reduced only for CD4 count<200 cells/μL (RR=0.4; 95% CI=0.2–0.9).

A similar analysis was performed for recent HIV RNA levels (Table 4). There was a trend of increasing RRs with higher recent HIV RNA levels for HIV-infected individuals (HIV-uninfected as reference group) for KS (P<0.001) and NHL (P<0.001). For lung cancer, the RR was significantly increased only for HIV RNA≥10,000 copies/mL, whereas for liver cancer the RR was significantly increased only for HIV RNA <500 copies/mL and for melanoma the RR was significantly increased for each HIV RNA category. Although there was a significant trend for oral cavity/pharynx cancers (P=0.017), it was not a clear dose-response relationship since the highest risk was for 501–9,999 copies/mL.

Table 5 presents relationships between recent CD4 and HIV RNA levels and cancer risk among HIV-infected individuals only, with mutual adjustment for CD4 count and HIV RNA. Compared with CD4≥500 cells/μl, CD4 ≤200 cells/μl was associated with a higher risk of each infection-related cancer; of the infection-unrelated cancers, colorectal cancer was significantly elevated for CD4 ≤200 compared with CD4≥500 cells/μl (RR: 4.8; 95% CI: 1.9, 12.3; P=0.001), while lung cancer had a borderline increased risk (RR: 2.0; 95% CI: 0.9, 4.1; P=0.07). Higher HIV RNA levels were associated with a higher risk of KS and NHL, but not other cancers.

DISCUSSION

In a large cohort of HIV-infected and demographically-similar HIV-uninfected individuals receiving care from the same healthcare system, we found that HIV-infected individuals had a higher risk for six of the ten cancer types examined (KS, NHL, HL, melanoma, anal cancer, and liver cancer), independent of several cancer risk factors. Except for melanoma, these cancer types have known viral etiologies. The risk for lung and oral cavity/pharynx cancers in HIV-infected individuals was elevated in demographic-adjusted analyses, but not after adjustment for the cancer risk factors smoking, alcohol/drug abuse and overweight/obesity. Further analysis suggested that immunodeficiency as measured by recent CD4 count was positively associated with the risk of all cancer types except prostate cancer, for which there was a suggestion of a negative association. Finally, there was little evidence for an association between recent HIV RNA levels and cancer risk, except for a positive association for KS and NHL.

The higher risk of cancer in HIV-infected individuals compared with the general population is well established, with substantially higher risk for cancers with known viral etiologies, such as anal cancer, HL, or AIDS-defining cancers (ADCs) (5, 17, 20–21). However, other cancer types, including lung, liver, and oral cavity/pharynx cancers, have much smaller elevated risks among HIV-infected individuals, which are more likely explained by the higher prevalence among HIV-infected individuals of traditional cancer risk factors, such as smoking (6–8), alcohol use (7, 9), and oncogenic virus coinfection (10–13). Here, we did in fact find that there was no overall increased risk of lung and oral cavity/pharynx cancers comparing HIV-infected and HIV-uninfected subjects after adjustment for smoking, alcohol/drug abuse and overweight/obesity. When each of these risk factors was considered alone, adjustment for smoking attenuated the rate ratio for HIV status slightly more than did adjustment for each of the other two potential confounders, although only adjustment for all three risk factors simultaneously resulted in a non-significant p-value for HIV infection status. These results suggest that the observed higher risk of these cancers in HIV-infected patients may be a result of several confounding factors. Alternatively, since these variables

are related, adjusting for all three confounders may reduce residual confounding that resulted from imperfect measurement. For example, those with an alcohol/drug abuse diagnosis were much more likely to be smokers (61%) compared with those without an alcohol/drug abuse diagnosis (26%).

For liver cancer, adjustment for smoking, alcohol (a known liver cancer risk factor)/drug abuse and overweight/obesity attenuated but did not eliminate the association. HBV and HCV infection status, which are established risk factors for liver cancer, were not included in adjusted models since HBV/HCV testing has become more routine for HIV-infected individuals, but is likely driven by clinical suspicion for HIV-uninfected individuals; thus adjusted estimates would likely be biased. Thus, because we did not adjust, it is possible that the observed elevated risk for liver cancer may be explained all or in part by the higher prevalence of HBV and HCV infection in HIV-infected individuals.

Finally, we also observed a decreased risk of prostate cancer with adjustment for demographics and other factors, consistent with prior studies (3, 20–21). The reason for the decreased prostate cancer risk is unknown, although some have attributed this observation to less screening in HIV patients (22).

Others have adjusted for cancer risk factors in comparisons of cancer risk in HIV-infected versus uninfected individuals. Several studies (23–26), for example, have indicated that the higher risk of lung cancer may be independent of smoking. Interestingly, our analysis did find a higher risk of lung cancer in the subgroup of HIV-infected individuals with low CD4 counts, independent of smoking and other risk factors. Thus, it is possible that the overall immune status of a cohort determines whether or not an overall elevated risk of lung cancer is found after adjustment for other risk factors.

Studies among U.S. Veterans have also been informative given the availability of an internal HIV-uninfected comparison group (17–18). One study indicated that adjustment for HCV infection and alcohol abuse/dependence explained all of the increased risk of liver cancer for HIV-infected individuals (18). Bedimo et al. (17) reported higher risks among HIV-infected U.S. Veterans for ADCs, HL, melanoma, and anal, lung and liver cancers compared with HIV-uninfected Veterans after adjustment for age, race and sex.

The strong, direct relationship between lower CD4 count and increased risk for KS and NHL among HIV-infected individuals is well-established (27–29). Similar observations for NADC and immunodeficiency are inconsistent likely due to the small numbers of cancer events, requiring analysis of grouped cancer types only (30–32), or often insensitive, static measures of CD4 count, such as CD4 count at AIDS diagnosis or at enrollment (1, 4, 6, 17, 24, 33–37). Several recent studies have evaluated time-dependent measures of CD4 count for specific cancers (14–16). In the multinational EuroSIDA cohort (14), lower recent CD4 count was independently associated with increased incidence of anal cancer, HL, and lung cancer. In the ATHENA cohort (15), longer exposure to CD4<200 cells/μL was associated with a higher risk of anal cancer, while lung and liver cancer were not related to immunodeficiency. Finally, in the French Hospital Database cohort (16), the largest study to date, recent low CD4 count was the best predictor of KS, NHL, HL, lung, liver, and cervical cancer incidence, whereas longer exposure to CD4 count <200 cells/μL predicted anal cancer risk.

With adjustment for several cancer risk factors, and inclusion of an HIV-uninfected comparison group, our study extends the findings of others regarding the association of immunodeficiency to a broad range of cancers. For ADC, even among HIV-infected individuals with CD4≥500 cells/μL, there remained a 60-fold higher risk for KS, but only a 4-fold higher risk for NHL compared with HIV-uninfected individuals. We also found here

that two NADCs with known viral etiology, anal cancer and HL, had significant trends of increasing risk (compared with HIV-uninfected individuals) with decreasing recent CD4 count, as did colorectal cancer, which is not known to be virus-related. Although trends were not significant, results also suggested an association between immunodeficiency and melanoma, as well as lung, liver and oral cavity/pharynx cancers. Analyses restricted to HIV-infected individuals supported these findings; all infection-related cancers were related to low CD4 count, while there was a suggestion of an association of low CD4 count with colorectal cancer, lung cancer, and melanoma. However, these observations require confirmation in other settings, particularly for colorectal cancer, which has not previously been linked to immunodeficiency.

The fact that most cancers associated with immunodeficiency have a known infectious cause suggests a mechanism in which an impaired immune system cannot adequately suppress human papillomavirus (HPV) (12), HCV (38), or other oncogenic virus infections, resulting in a higher risk of related cancers. Another possibility is that the impaired immune system may result in reduced immune surveillance for malignant cells (39), possibly explaining the associations observed for lung cancer, colorectal cancer, and melanoma. It is also conceivable that these cancer types have an as yet unidentified infectious cause. One study, for example, indicated that recurrent pneumonia was a risk factor for lung cancer in AIDS cases, suggesting a role of chronic infection (40).

HIV infection prior to ART is characterized by a chronically activated but impaired immune system (41–43), which could conceivably contribute to the elevated risk of certain cancers. Higher HIV RNA levels has been used as a proxy for immune activation (44), and has been linked to higher risk for ADCs, but not NADCs (16, 30, 37, 45). The French Hospital Database cohort (16), however, did note a higher risk of anal cancer with longer duration of HIV RNA>100,000 copies/mL. Here, we observed that higher recent HIV RNA levels were associated with KS and NHL incidence, and suggestively, with lung cancer and melanoma, but not with any other cancer type. In models among HIV-infected individuals, only KS and NHL remained associated with higher HIV RNA levels with adjustment for recent CD4 count and other potential risk factors.

Our study had several limitations. First, the risk factors considered were obtained from routine clinical practice, and not in a standardized fashion. Smoking, for example, was captured during outpatient visit encounters, and only routinely in more recent years. The level of detail recorded for risk factors only allowed for broad categorizations (e.g., ever or never smoked). Alcohol/drug abuse diagnoses did not capture actual alcohol or drug *use* among health plan members. Those without documentation of these risk factors in their medical record were considered unexposed. Although each of these exposure measurement issues may have resulted in residual confounding, as discussed, adjustment for the potential confounders together may have overcome some of the residual confounding. Finally, we were unable to adjust for other known cancer risk factors for which sufficient data were not available, such as diet, sun exposure, and infection by HPV, HBV, and HCV.

Regarding race/ethnicity, 94% of HIV-infected health plan members, but only 57% of HIV-uninfected members, had recorded race/ethnicity. However, since HIV-uninfected subjects were matched to HIV-infected subjects by medical center, differences in race/ethnicity between groups were likely mitigated. In fact, our prior work in the same study population (5) indicated that multiple imputation for missing race/ethnicity did not affect inferences for effect of HIV infection status on cancer risk. Despite the large sample size, another limitation was the inability to study less common cancers, or evaluate more refined CD4 count or HIV RNA categories.

The major strength of our study was the inclusion of large, well-characterized populations of HIV-infected individuals and matched, demographically-similar HIV-uninfected individuals from the same health care system. Another key strength was the high quality ascertainment of HIV infection status and cancer diagnoses from long-standing registries. In addition, information about several key risk factors was obtained from the KP electronic medical record. Finally, the study results are likely to be highly generalizable to those with access to healthcare since KP provides care to approximately 30% of all insured Californians in its most populated areas (19). However, study results may have limited generalizability to women, or to those without access to healthcare.

In summary, this was one of the few studies to directly compare the risk of cancer in HIV-infected individuals with a demographically-similar, HIV-uninfected, internal comparison group, adjusting for several major cancer risk factors. The higher risk of infection-related cancers was confirmed, especially with more advanced immunodeficiency. The higher risk for certain NADCs, including lung, oral cavity/pharynx and liver cancers was explained in large part by traditional risk factors, but risk remained elevated for individuals with more advanced HIV/AIDS. We also revealed a possible increased risk for colorectal cancer for HIV-infected individuals with more advanced HIV/AIDS. Our observations that most cancers were either no longer elevated in HIV-infected individuals at CD4≥500 cells/μL compared with HIV-uninfected individuals, or had greatly attenuated risks supports the concept of earlier initiation of ART to maintain high CD4 levels. Such a strategy would not only reduce the risk of AIDS or death (46–48), but may also reduce the burden of a wide range of cancer types. However, our observation that much of the increased risk for lung, oral cavity/pharynx, and liver cancer was attributed to traditional cancer risk factors implies that traditional risk factor reduction approaches, including smoking cessation and alcohol moderation, remain the most important strategies for reducing the burden of these cancers.

Acknowledgments

We thank Leo Hurley for helpful reviews, and Michele Manos and Valentina Shvachko of the KPNC Viral Hepatitis Registry.

Financial support: This research was supported by research grants from the Garfield Memorial Research Fund and Pfizer Pharmaceuticals. MJS was supported by grant number K01AI071725 from the NIAID, and RD was supported by grant number U10-AA13566 from the NIAAA.

REFERENCES

1. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. J Natl Cancer Inst. 2009 Aug 19; 101(16):1120–1130. 2728745. [PubMed: 19648510]
2. 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 Dec; 52(5):611–622. PMC2790038. [PubMed: 19770804]
3. Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman AC, Tong TC, 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 May 20; 148(10):728–736. [PubMed: 18490686]
4. Engels EA, Biggar RJ, Hall HI, Cross H, Crutchfield A, Finch JL, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. Int J Cancer. 2008 Jul 1; 123(1): 187–194. [PubMed: 18435450]
5. Silverberg MJ, Chao C, Leyden WA, Xu L, Tang B, Horberg MA, et al. HIV infection and the risk of cancers with and without a known infectious cause. AIDS. 2009 Nov 13; 23(17):2337–2345. PMC2863991. [PubMed: 19741479]

6. Clifford GM, Polesel J, Rickenbach M, Dal Maso L, Keiser O, Kofler A, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J Natl Cancer Inst. 2005 Mar 16; 97(6):425–432. [PubMed: 15770006]
7. Hessol NA, Seaberg EC, Preston-Martin S, Massad LS, Sacks HS, Silver S, et al. Cancer risk among participants in the Women's Interagency HIV Study. J Acquir Immune Defic Syndr. 2004 Aug 1; 36(4):978–985. [PubMed: 15220706]
8. Phelps RM, Smith DK, Heilig CM, Gardner LI, Carpenter CC, Klein RS, et al. Cancer incidence in women with or at risk for HIV. Int J Cancer. 2001 Dec 1; 94(5):753–757. [PubMed: 11745473]
9. Murillas J, Del Rio M, Riera M, Vaquer P, Salas A, Leyes M, et al. Increased incidence of hepatocellular carcinoma (HCC) in HIV-1 infected patients. Eur J Intern Med. 2005; 16(2):113–115. [PubMed: 15833677]
10. Evans, AS.; Kaslow, RA. Viral Infections of Humans: Epidemiology and Control. 4th edition. New York and London: Plenum Medical Book Company; 2006.
11. Martin JN, Ganem DE, Osmond DH, Page-Shafer KA, Macrae D, Kedes DH. Sexual transmission and the natural history of human herpesvirus 8 infection. N Engl J Med. 1998; 338(14):948–954. [PubMed: 9521982]
12. Palefsky JM, Minkoff H, Kalish LA, Levine A, Sacks HS, Garcia P, et al. Cervicovaginal human papillomavirus infection in human immunodeficiency virus-1 (HIV)-positive and high-risk HIV-negative women. J Natl Cancer Inst. 1999; 91(3):226–236. [PubMed: 10037100]
13. Vallet-Pichard A, Pol S. Hepatitis viruses and human immunodeficiency virus co-infection: pathogenesis and treatment. J Hepatol. 2004; 41(1):156–166. [PubMed: 15246224]
14. Reekie J, Kosa C, Engsig F, Monforte A, Wiercinska-Drapalo A, Domingo P, et al. Relationship between current level of immunodeficiency and non-acquired immunodeficiency syndrome-defining malignancies. Cancer. 2010 Nov 15; 116(22):5306–5315. [PubMed: 20661911]
15. Kesselring A, Gras L, Smit C, van Twillert G, Verbon A, de Wolf F, et al. Immunodeficiency as a Risk Factor for Non-AIDS-Defining Malignancies in HIV-1-Infected Patients Receiving Combination Antiretroviral Therapy. Clin Infect Dis. 2011 Jun; 52(12):1458–1465. [PubMed: 21628488]
16. Guiguet M, Boue F, Cadranel J, Lang JM, Rosenthal E, Costagliola D. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. Lancet Oncol. 2009 Dec; 10(12): 1152–1159. [PubMed: 19818686]
17. Bedimo RJ, McGinnis KA, Dunlap M, Rodriguez-Barradas MC, Justice AC. Incidence of Non-AIDS-Defining Malignancies in HIV-Infected Versus Noninfected Patients in the HAART Era: Impact of Immunosuppression. J Acquir Immune Defic Syndr. 2009 Jul 16; 52(2):203–208. [PubMed: 19617846]
18. McGinnis KA, Fultz SL, Skanderson M, Conigliaro J, Bryant K, Justice AC. Hepatocellular carcinoma and non-Hodgkin's lymphoma: the roles of HIV, hepatitis C infection, and alcohol abuse. J Clin Oncol. 2006 Nov 1; 24(31):5005–5009. [PubMed: 17075119]
19. Gordon NP. How Does the Adult Kaiser Permanente Membership in Northern California Compare with the Larger Community? 2006 Available at: http://www.dor.kaiser.org/external/uploadedFiles/content/research/mhs/_2011_Revised_Site/Documents_Special_Reports/comparison_kaiser_vs_nonKaiser_adults_kpnc(1).pdf.
20. Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM, et al. Trends in cancer risk among people with AIDS in the United States 1980–2002. AIDS. 2006 Aug 1; 20(12):1645–1654. [PubMed: 16868446]
21. 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 Jul 7; 370(9581):59–67. [PubMed: 17617273]
22. 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 Nov; 19(11):2910–2915. 2976800. [PubMed: 20837717]

23. Kirk GD, Merlo C, P OD, Mehta SH, Galai N, Vlahov D, et al. HIV infection is associated with an increased risk for lung cancer, independent of smoking. Clin Infect Dis. 2007 Jul 1; 45(1):103–110. [PubMed: 17554710]
24. Chaturvedi AK, Pfeiffer RM, Chang L, Goedert JJ, Biggar RJ, Engels EA. Elevated risk of lung cancer among people with AIDS. AIDS. 2007 Jan 11; 21(2):207–213. [PubMed: 17197812]
25. Engels EA, Brock MV, Chen J, Hooker CM, Gillison M, Moore RD. Elevated incidence of lung cancer among HIV-infected individuals. J Clin Oncol. 2006 Mar 20; 24(9):1383–1388. [PubMed: 16549832]
26. Shiels MS, Cole SR, Mehta SH, Kirk GD. Lung cancer incidence and mortality among HIV-infected and HIV-uninfected injection drug users. J Acquir Immune Defic Syndr. 2010 Dec; 55(4): 510–515. 2974802. [PubMed: 20838223]
27. Clifford GM, Franceschi S. Cancer risk in HIV-infected persons: influence of CD4(+) count. Future Oncol. 2009 Jun; 5(5):669–678. [PubMed: 19519206]
28. Franceschi S, Maso LD, Rickenbach M, Polesel J, Hirschel B, Cavassini M, et al. Kaposi sarcoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. Br J Cancer. 2008 Sep 2; 99(5):800–804. [PubMed: 18665172]
29. Polesel J, Clifford GM, Rickenbach M, Dal Maso L, Battegay M, Bouchardy C, et al. Non-Hodgkin lymphoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. AIDS. 2008 Jan 11; 22(2):301–306. [PubMed: 18097233]
30. Bruyand M, Thiebaut R, Lawson-Ayayi S, Joly P, Sasco AJ, Mercie P, et al. Role of uncontrolled HIV RNA level and immunodeficiency in the occurrence of malignancy in HIV-infected patients during the combination antiretroviral therapy era: Agence Nationale de Recherche sur le Sida (ANRS) CO3 Aquitaine Cohort. Clin Infect Dis. 2009 Oct 1; 49(7):1109–1116. [PubMed: 19705973]
31. Prosperi MC, Cozzi-Lepri A, Castagna A, Mussini C, Murri R, Giacometti A, et al. Incidence of malignancies in HIV-infected patients and prognostic role of current CD4 cell count: evidence from a large Italian cohort study. Clin Infect Dis. May 1; 50(9):1316–1321. [PubMed: 20297953]
32. Krishnan S, Schouten JT, Jacobson DL, Benson CA, Collier AC, Koletar SL, et al. Incidence of Non-AIDS-Defining Cancer in Antiretroviral Treatment-Naive Subjects after Antiretroviral Treatment Initiation: An ACTG Longitudinal Linked Randomized Trials Analysis. Oncology. 2011 May 23; 80(1–2):42–49. [PubMed: 21606663]
33. Biggar RJ, Jaffe ES, Goedert JJ, Chaturvedi A, Pfeiffer R, Engels EA. Hodgkin lymphoma and immunodeficiency in persons with HIV/AIDS. Blood. 2006 Dec 1; 108(12):3786–3791. [PubMed: 16917006]
34. Clifford GM, Rickenbach M, Polesel J, Dal Maso L, Steffen I, Ledergerber B, et al. Influence of HIV-related immunodeficiency on the risk of hepatocellular carcinoma. AIDS. 2008 Oct 18; 22(16):2135–2141. [PubMed: 18832877]
35. Burgi A, Brodine S, Wegner S, Milazzo M, Wallace MR, Spooner K, et al. Incidence and risk factors for the occurrence of non-AIDS-defining cancers among human immunodeficiency virus-infected individuals. Cancer. 2005 Oct 1; 104(7):1505–1511. [PubMed: 16104038]
36. Clifford GM, Rickenbach M, Lise M, Dal Maso L, Battegay M, Bohlius J, et al. Hodgkin lymphoma in the Swiss HIV Cohort Study. Blood. 2009 Jun 4; 113(23):5737–5742. [PubMed: 19336755]
37. Crum-Cianflone N, Hullsiek KH, Marconi V, Weintrob A, Ganesan A, Barthel RV, et al. Trends in the incidence of cancers among HIV-infected persons and the impact of antiretroviral therapy: a 20-year cohort study. AIDS. 2009 Jan 2; 23(1):41–50. [PubMed: 19050385]
38. Rauch A, Gaudieri S, Evison J, Nolan D, Cavassini M, Weber R, et al. Low current and nadir CD4+ T-cell counts are associated with higher hepatitis C virus RNA levels in the Swiss HIV cohort study. Antivir Ther. 2008; 13(3):455–460. [PubMed: 18572759]
39. Burnet FM. The concept of immunological surveillance. Prog Exp Tumor Res. 1970; 13:1–27. [PubMed: 4921480]
40. Shebl FM, Engels EA, Goedert JJ, Chaturvedi AK. Pulmonary infections and risk of lung cancer among persons with AIDS. J Acquir Immune Defic Syndr. 2010 Nov 1; 55(3):375–379. 2955766. [PubMed: 20736841]

41. French MA, King MS, Tschampa JM, da Silva BA, Landay AL. Serum immune activation markers are persistently increased in patients with HIV infection after 6 years of antiretroviral therapy despite suppression of viral replication and reconstitution of CD4+ T cells. J Infect Dis. 2009 Oct 15; 200(8):1212–1215. [PubMed: 19728788]

42. Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med. 2008 Oct 21.5(10):e203. 2570418. [PubMed: 18942885]

43. Neuhaus J, Jacobs DR Jr, Baker JV, Calmy A, Duprez D, La Rosa A, et al. Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. J Infect Dis. 2010 Jun 15; 201(12):1788–1795. 2872049. [PubMed: 20446848]

44. Landay A, Benning L, Bremer J, Weiser B, Burger H, Nowicki M, et al. Correlates of immune activation marker changes in human immunodeficiency virus (HIV)-seropositive and high-risk HIV-seronegative women who use illicit drugs. J Infect Dis. 2003 Jul 15; 188(2):209–218. [PubMed: 12854075]

45. Monforte A, Abrams D, Pradier C, Weber R, Reiss P, Bonnet F, et al. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. AIDS. 2008 Oct 18; 22(16):2143–2153. [PubMed: 18832878]

46. When to Initiate Combined Antiretroviral Therapy to Reduce Mortality and AIDS-Defining Illness in HIV-Infected Persons in Developed Countries: An Observational Study. Ann Intern Med. 2011 Apr 19; 154(8):509–515. [PubMed: 21502648]

47. Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med. 2009 Apr 30; 360(18): 1815–1826. PMC2854555. [PubMed: 19339714]

48. Sterne JA, May M, Costagliola D, de Wolf F, Phillips AN, Harris R, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. Lancet. 2009 Apr 18; 373(9672):1352–1363. [PubMed: 19361855]

Table 1

Cohort baseline characteristics

	HIV-infected (n=20,775)	HIV-uninfected (n=215,158)	P-value
Sex, %			0.65
Male	90.5	90.4	
Female	9.5	9.6	
Mean age (SD)	40.6 (9.8)	40.1 (10.1)	<0.001
Race/ethnicity (among known), %			<0.001
White	55.0	46.0	
Black/African-American	18.6	11.6	
Hispanic/Latino	21.5	26.8	
Asian/Pacific Islander	4.1	13.3	
Other	0.7	2.2	
% unknown of total	6.4	42.9	
Ever known hepatitis C virus infection, %	7.7	1.1	<0.001
Ever known hepatitis B virus infection, %	4.6	0.6	<0.001
Ever tobacco use, %	42.5	27.5	<0.001
Ever alcohol abuse, %	11.2	6.2	<0.001
Ever other drug abuse, %	15.8	4.7	<0.001
Ever overweight/obese, %	37.5	42.1	<0.001
HIV exposure risk, %			
Men who have sex with men	59.4	n/a	
Injection drug use	5.8		
Heterosexual	12.7		
Other	1.2		
Unknown	20.9		
Mean CD4 count (SD), cells/μL	396 (286)	n/a	
Mean log HIV RNA level (SD), copies/mL	4.7 (5.0)	n/a	
Prior AIDS diagnosis	40.7	n/a	
Prior use of ART	47.1	n/a	

ART, antiretroviral therapy; SD, standard deviation

Table 2

Cancer incidence rates, and rate ratios by HIV infection status

	HIV+		HIV−		Demographic-adjusted[b]		Fully-adjusted[b]	
	n	rate[a]	n	rate[a]	RR (95% CI)	P	RR (95% CI)	P
Infection-related								
Kaposi sarcoma	525	604	34	3	197.1 (139.2, 279.0)	<0.001	196.0 (138.1, 278.0)	<0.001
Non-Hodgkin lymphoma	241	269	193	17	15.9 (13.2, 19.3)	<0.001	15.4 (12.7, 18.7)	<0.001
Anal	86	96	18	2	60.9 (36.6, 101.4)	<0.001	55.7 (33.2, 93.4)	<0.001
Hodgkin lymphoma	52	58	32	3	19.8 (12.7, 31.0)	<0.001	18.7 (11.8, 29.5)	<0.001
Oral cavity/pharynx	26	29	183	16	1.9 (1.3, 2.9)	0.002	1.4 (0.9, 2.1)	0.14
Liver	24	27	110	10	2.6 (1.7, 4.0)	<0.001	1.8 (1.1, 2.8)	0.012
Infection-unrelated								
Prostate	91	112	1,398	138	0.8 (0.6, 0.9)	0.012	0.8 (0.6, 0.9)	0.012
Lung	56	62	380	34	1.8 (1.4, 2.4)	<0.001	1.2 (0.9, 1.6)	0.15
Colorectal	35	39	459	41	0.9 (0.6, 1.3)	0.55	0.9 (0.6, 1.2)	0.34
Melanoma	34	38	266	24	1.8 (1.3, 2.6)	0.001	1.8 (1.3, 2.6)	0.001

RR, rate ratio

[a] Crude incidence rate per 100,000 person-years

[b] RR comparing cancer incidence in HIV-infected individuals with HIV-uninfected individuals (reference group) from Poisson regression models. Demographic-adjusted model included terms for HIV status, age, sex, race/ethnicity, calendar period, and KP region. Fully-adjusted model also included terms for smoking, overweight, and alcohol/drug abuse.

Table 3

Rate ratios[a] (95% CI) for cancer by recent CD4 among HIV-infected compared with HIV-uninfected subjects

	Recent CD4 cells/μL			
	≤200	201–499	≥500	p-trend[b]
Infection-related				
Kaposi sarcoma	741.1 (517.0, 1062.3)	133.6 (91.9, 194.2)	59.9 (39.3, 91.5)	<0.001
Non-Hodgkin lymphoma	50.8 (40.0, 64.7)	14.2 (11.1, 18.1)	3.9 (2.5, 6.0)	<0.001
Anal	91.5 (48.0, 174.5)	63.4 (36.4, 110.3)	33.8 (17.8, 64.3)	0.005
Hodgkin lymphoma	55.3 (31.3, 97.9)	12.2 (6.5, 22.8)	13.5 (7.2, 25.1)	<0.001
Oral cavity/pharynx	2.5 (1.2, 5.4)	1.6 (0.9, 2.7)	0.7 (0.3, 1.7)	0.065
Liver	2.9 (1.2, 6.6)	2.1 (1.2, 3.7)	1.0 (0.4, 2.4)	0.17
Infection-unrelated				
Prostate	0.4 (0.2, 0.9)	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	0.21
Lung	2.2 (1.3, 3.6)	1.0 (0.6, 1.5)	1.2 (0.7, 1.9)	0.078
Colorectal	1.8 (1.0, 3.3)	0.8 (0.5, 1.3)	0.6 (0.3, 1.1)	0.028
Melanoma	2.1 (0.8, 5.0)	2.5 (1.6, 3.9)	1.1 (0.5, 2.1)	0.092

[a] RRs from Poisson regression models with terms for HIV status/CD4 (HIV-uninfected reference group), age, sex, race/ethnicity, calendar period, KP region, smoking, overweight, and alcohol/drug abuse.

[b] P-value tests trend in RRs over CD4 strata by the likelihood ratio test..

Table 4

Rate ratios (95% CI)[a] for cancer by recent HIV RNA among HIV-infected compared with HIV-uninfected subjects

	Recent HIV RNA copies/mL			
	≥10,000	501–9,999	≤500	p-trend[b]
Infection-related				
Kaposi sarcoma	538.1 (376.4, 769.2)	103.0 (66.0, 160.7)	78.6 (53.5, 115.3)	<0.001
Non-Hodgkin lymphoma	48.3 (38.5, 60.7)	14.0 (9.6, 20.4)	6.1 (4.5, 8.1)	<0.001
Anal	51.8 (25.9, 103.3)	48.1 (22.9, 101.1)	58.7 (34.3, 100.5)	0.79
Hodgkin lymphoma	24.7 (13.0, 46.7)	11.5 (4.4, 29.8)	18.4 (11.1, 30.4)	0.30
Oral cavity/pharynx	0.3 (0.0, 2.0)	2.8 (1.4, 5.8)	1.4 (0.8, 2.2)	0.017
Liver	1.7 (0.6, 4.5)	0.6 (0.1, 4.1)	2.1 (1.3, 3.4)	0.30
Infection-unrelated				
Prostate	0.5 (0.3, 0.9)	0.5 (0.2, 1.0)	0.9 (0.7, 1.1)	0.077
Lung	1.8 (1.1, 3.1)	1.2 (0.6, 2.5)	1.1 (0.8, 1.6)	0.32
Colorectal	0.5 (0.2, 1.4)	0.5 (0.2, 1.6)	1.0 (0.7, 1.5)	0.27
Melanoma	2.6 (1.3, 5.1)	2.2 (1.0, 5.0)	1.5 (1.0, 2.4)	0.39

[a] RRs from Poisson regression models with terms for HIV status/HIV RNA (HIV-uninfected reference group), age, sex, race/ethnicity, calendar period, KP region, smoking, overweight, and alcohol/drug abuse.

[b] P-value tests trend in RRs over HIV RNA strata by the likelihood ratio test.

Table 5

Rate ratios (95% CI)[a] for cancer by recent CD4 and HIV RNA among HIV-infected subjects

	Recent CD4 cells/μL		Recent HIV RNA copies/mL	
	≤200	201–499	≥10,000	501–9,999
Infection-related				
Kaposi sarcoma	7.5 (5.6, 10.2)	1.9 (1.4, 2.5)	3.8 (3.0, 4.8)	1.2 (0.8, 1.7)
Non-Hodgkin lymphoma	6.8 (4.2, 10.9)	2.9 (1.8, 4.6)	4.4 (3.2, 6.2)	1.9 (1.2, 2.9
Anal	3.1 (1.6, 6.1)	2.0 (1.2, 3.4)	0.7 (0.4, 1.3)	0.7 (0.4, 1.4)
Hodgkin lymphoma	3.7 (1.8, 7.8)	0.9 (0.4, 1.8)	0.9 (0.4, 1.8)	0.6 (0.2, 1.6)
Oral cavity/pharynx	5.9 (1.8, 19.4)	2.6 (0.9, 7.4)	0.2 (0.0, 1.3)	1.9 (0.8, 4.6)
Liver	4.3 (1.2, 15.0)	2.5 (0.9, 7.1)	0.4 (0.1, 1.5)	0.2 (0.0, 1.5)
Infection-unrelated				
Prostate	0.7 (0.3, 1.6)	1.1 (0.7, 1.7)	0.5 (0.2, 1.1)	0.5 (0.2, 1.1)
Lung	2.0 (0.9, 4.1)	0.9 (0.5, 1.6)	0.9 (0.4, 1.9)	0.9 (0.4, 2.1)
Colorectal	4.8 (1.9, 12.3)	1.7 (0.7, 3.9)	0.5 (0.1, 1.4)	0.6 (0.2, 1.9)
Melanoma	1.8 (0.6, 6.0)	2.3 (1.0, 5.3)	1.9 (0.8, 4.6)	1.5 (0.6, 3.8)

[a] RRs from Poisson regression models with terms for recent CD4 (reference: ≥500 cells/μl), recent HIV RNA (reference: ≤500 copies/ml), age, sex, race/ethnicity, calendar period, KP region, smoking, overweight, alcohol/drug abuse, prior antiretroviral therapy use, HIV risk, and years known HIV-infected.