Published OnlineFirst November 22, 2011; DOI:10.1158/1055-9965.EPI-11-0777

Cancer Epidemiology, Biomarkers & Prevention

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

Michael J. Silverberg, Chun Chao, Wendy A. Leyden, et al.

Cancer Epidemiol Biomarkers Prev 2011;20:2551-2559. Published OnlineFirst November 22, 2011.

Published OnlineFirst November 22, 2011; DOI:10.1158/1055-9965.EPI-11-0777

Cancer Epidemiology, Biomarkers & Prevention

Research Article

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]

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 to 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.

Impact: Earlier antiretroviral therapy initiation to maintain high CD4 levels might reduce the burden of cancer in this population. *Cancer Epidemiol Biomarkers Prev; 20(12); 2551–9. ©2011 AACR.*

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 NADC incidence rates in HIV-infected versus demographically similar HIV-uninfected

Authors' Affiliations: [1]Kaiser Permanente Northern California, Oakland, California; [2]Kaiser Permanente Southern California, Pasadena, California; [3]Mid-Atlantic Permanente Research Institute, Rockville, Maryland; [4]Kaiser Permanente Northern California, Hayward, California; [5]Kaiser Permanente Southern California, Los Angeles, California; [6]Yale School of Public Health and School of Medicine, New Haven, Connecticut; and [7]San Francisco General Hospital and [8]University of California San Francisco, San Francisco, California

Corresponding Author: Michael J. Silverberg, Kaiser Permanente Northern California, Division of Research, 2000 Broadway, Oakland, CA 94612. Phone: 510-891-3801; Fax: 510-891-3508; E-mail: Michael.J.Silverberg@kp.org

doi: 10.1158/1055-9965.EPI-11-0777

Published OnlineFirst November 22, 2011; DOI:10.1158/1055-9965.EPI-11-0777

subjects from the same health care 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 6 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 HIV-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 only way to classify these factors in our data because 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, and ≥500 cells/μL) and HIV RNA (≥10,000, 501–9,999, and ≤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, and 65+ years) and calendar period (1996–1998, 1999–2001, 2002–2004, and 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 that 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

Published OnlineFirst November 22, 2011; DOI:10.1158/1055-9965.EPI-11-0777

of the RR for HIV infection status with lower CD4 counts among HIV-infected individuals was assessed by the likelihood ratio test. Similarly, in a separate model, we then 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 were 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 done with SAS (Version 9.1), 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

Table 1. Cohort baseline characteristics

	HIV$^+$ (n = 20,775)	HIV$^-$ (n = 215,158)	P
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 race/ethnicity 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	

Abbreviation: SD, standard deviation.

Published OnlineFirst November 22, 2011; DOI:10.1158/1055-9965.EPI-11-0777

Table 2. Cancer incidence rates and RRs 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

[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.

3 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

Table 3. RRs[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 (517.0–1,062.3)	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.

Published OnlineFirst November 22, 2011; DOI:10.1158/1055-9965.EPI-11-0777

for lower CD4 count levels). Specifically, for the 2 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 to 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 done 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 because the highest risk was for 501 to 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; $P = 0.001$), whereas 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 health care system, we found that HIV-infected individuals had a higher risk for 6 of the 10 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 such as 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 (ADC; refs. 5, 17, 20, 21). However, other cancer

Table 4. RRs (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.

Published OnlineFirst November 22, 2011; DOI:10.1158/1055-9965.EPI-11-0777

Table 5. RRs (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 ART use, HIV risk, and years known HIV infected.

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 RR for HIV status slightly more than did adjustment for each of the other 2 potential confounders, although only adjustment for all 3 risk factors simultaneously resulted in a nonsignificant *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, because these variables are related, adjusting for all 3 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 because 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 and colleagues (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

Published OnlineFirst November 22, 2011; DOI:10.1158/1055-9965.EPI-11-0777

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, whereas 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 2 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, and 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; ref. 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.

With regard to race/ethnicity, 94% of HIV-infected health plan members, but only 57% of HIV-uninfected members, had recorded race/ethnicity. However, because 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 the 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 health care. However, study results may have limited generalizability to women, or to those without access to health care.

Published OnlineFirst November 22, 2011; DOI:10.1158/1055-9965.EPI-11-0777

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 $\geq$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.

Disclosure of Potential Conflicts of Interest

The authors report commercial research grant support from Pfizer (M.J. Silverberg, C. Chao, W.A. Leyden, L. Xu, M.A. Horberg, D. Klein, W.J. Towner, C.P. Quesenberry, Jr.), Merck (M.J. Silverberg, C. Chao, M.A. Horberg, W.J. Towner, C.P. Quesenberry, Jr.), Gilead (D. Klein, W.J. Towner) and Tibotec (W.J. Towner). No other conflicts were reported.

Acknowledgments

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

Grant Support

This research was supported by research grants from the Garfield Memorial Research Fund and Pfizer Pharmaceuticals. M.J. Silverberg was supported by grant number K01AI071725 from the NIAID, and R. Dubrow was supported by grant number U10-AA13566 from the NIAAA.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received August 12, 2011; revised September 26, 2011; accepted October 15, 2011; published OnlineFirst November 22, 2011.

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;101:1120–30.
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;52:611–22.
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;148:728–36.
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;123:187–94.
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;23:2337–45.
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;97:425–32.
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;36:978–85.
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;94:753–7.
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;16:113–5.
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;338:948–54.
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;91:226–36.
13. Vallet-Pichard A, Pol S. Hepatitis viruses and human immunodeficiency virus co-infection: pathogenesis and treatment. J Hepatol 2004;41:156–66.
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;116:5306–15.
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;52:1458–65.
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;10:1152–9.
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;52:203–8.
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;24:5005–9.
19. Gordon NP. How does the adult Kaiser Permanente Membership in Northern California compare with the larger community? 2006; [cited August 10, 2011]. 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;20:1645–54.

Published OnlineFirst November 22, 2011; DOI:10.1158/1055-9965.EPI-11-0777

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;370:59–67.
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;19:2910–5.
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;45:103–10.
24. Chaturvedi AK, Pfeiffer RM, Chang L, Goedert JJ, Biggar RJ, Engels EA. Elevated risk of lung cancer among people with AIDS. AIDS 2007;21:207–13.
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;24:1383–8.
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;55:510–5.
27. Clifford GM, Franceschi S. Cancer risk in HIV-infected persons: influence of CD4(+) count. Future Oncol 2009;5:669–78.
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;99:800–4.
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;22:301–6.
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;49:1109–16.
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 50:1316–21.
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;80:42–9.
33. Biggar RJ, Jaffe ES, Goedert JJ, Chaturvedi A, Pfeiffer R, Engels EA. Hodgkin lymphoma and immunodeficiency in persons with HIV/AIDS. Blood 2006;108:3786–91.
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;22:2135–41.
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;104:1505–11.
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;113:5737–42.
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;23:41–50.
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;13:455–60.
39. Burnet FM. The concept of immunological surveillance. Prog Exp Tumor Res 1970;13:1–27.
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;55:375–9.
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;200:1212–5.
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;5:e203.
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;201:1788–95.
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;188:209–18.
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;22:2143–53.
46. HIV-CAUSAL Collaboration Cain LE, Logan R, Robins JM, Sterne JA, Sabin C, et al. 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;154:509–15.
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;360:1815–26.
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;373:1352–63.