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

Michael J. Silverberg1, Chun Chao2, Wendy A. Leyden1, Lanfang Xu2, Michael A. Horberg3, Daniel Klein4, William J. Towner5, Robert Dubrow6, Charles P. Quesenberry, Jr1, Romain S. Neugebauer1, and Donald I. Abrams7,8

General Hospital and University of California San Francisco, San Francisco, California, Division of Research, 2000 Broadway, Oakland, CA 94612. Corresponding Author: Michael J. Silverberg, Kaiser Permanente Northern California, Oakland, California; 2Kaiser Permanente Southern California, Los Angeles, California; 3Kaiser Permanente Southern California, Hayward, California; 4Kaiser 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 RR 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); 1–9. ©2011 AACR.
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
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 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

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

Abbreviation: SD, standard deviation.
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 $\leq 500$ cells/$\mu$L (although the RR was substantially lower than

### Table 2. Cancer incidence rates and RRs by HIV infection status

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

$^a$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. RRs$^a$ (95% CI) for cancer by recent CD4 among HIV-infected compared with HIV-uninfected subjects

<table>
<thead>
<tr>
<th></th>
<th>$\leq 200$</th>
<th>$201–499$</th>
<th>$\geq 500$</th>
<th>$P_{\text{trend}}$ $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>741.1 (517.0–1,062.3)</td>
<td>133.6 (91.9–194.2)</td>
<td>59.9 (39.3–91.5)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>50.8 (40.0–64.7)</td>
<td>14.2 (11.1–18.1)</td>
<td>3.9 (2.5–6.0)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Anal</td>
<td>91.5 (48.0–174.5)</td>
<td>63.4 (36.4–110.3)</td>
<td>33.8 (17.8–64.3)</td>
<td>0.005</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>55.3 (31.3–97.9)</td>
<td>12.2 (6.5–22.8)</td>
<td>13.5 (7.2–25.1)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Oral cavity/pharynx</td>
<td>2.5 (1.2–5.4)</td>
<td>1.6 (0.9–2.7)</td>
<td>0.7 (0.3–1.7)</td>
<td>0.065</td>
</tr>
<tr>
<td>Liver</td>
<td>2.9 (1.2–6.6)</td>
<td>2.1 (1.2–3.7)</td>
<td>1.0 (0.4–2.4)</td>
<td>0.17</td>
</tr>
<tr>
<td>Infection unrelated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>0.4 (0.2–0.9)</td>
<td>0.8 (0.6–1.1)</td>
<td>0.8 (0.6–1.1)</td>
<td>0.21</td>
</tr>
<tr>
<td>Lung</td>
<td>2.2 (1.3–3.6)</td>
<td>1.0 (0.6–1.5)</td>
<td>1.2 (0.7–1.9)</td>
<td>0.078</td>
</tr>
<tr>
<td>Colorectal</td>
<td>1.8 (1.0–3.3)</td>
<td>0.8 (0.5–1.3)</td>
<td>0.6 (0.3–1.1)</td>
<td>0.028</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2.1 (0.8–5.0)</td>
<td>2.5 (1.6–3.9)</td>
<td>1.1 (0.5–2.1)</td>
<td>0.092</td>
</tr>
</tbody>
</table>

$^a$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.
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>
<thead>
<tr>
<th>Table 4. RRs (95% CI)(^a) for cancer by recent HIV RNA among HIV-infected compared with HIV-uninfected subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recent HIV RNA copies/mL</strong></td>
</tr>
<tr>
<td><strong>≥10,000</strong></td>
</tr>
<tr>
<td>Infection related</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Anal</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>Oral cavity/pharynx</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Infection unrelated</td>
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<td>Prostate</td>
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<td>Lung</td>
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<td>Colorectal</td>
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<td>Melanoma</td>
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\( ^a\)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.
individuals; thus adjusted estimates would likely be
likely driven by clinical suspicion for HIV-uninfected
become more routine for HIV-infected individuals but is
adjusted models because HBV/HCV testing has
established risk factors for liver cancer, were not included
association. HBV and HCV infection status, which are
weight/obesity attenuated, but did not eliminate, the
known liver cancer risk factor)/drug abuse, and over-
abuse diagnosis (26%).
(61%), compared with those without an alcohol/drug
abuse diagnosis were much more likely to be smokers
measurement. For example, those with an alcohol/drug
reduce residual confounding that resulted from imperfect
confounding factors. Alternatively, because these vari-
cancers in HIV-infected patients may be a result of several
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 vari-
ables are related, adjusting for all 3 confounders may
result in 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 over-
weight/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 fac-
tors, 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 compar-
isons 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
indicated that the higher risk of lung cancer may be
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 vari-
es, 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
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individuals; thus adjusted estimates would likely be

| 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) |

aRRs 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.
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.
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.

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.

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References

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