HIV Infection, Immunosuppression, and Age at Diagnosis of Non-AIDS-Defining Cancers

Meredith S. Shiels,[1] Keri N. Althoff,[2] Ruth M. Pfeiffer,[1] Chad J. Achenbach,[3] Alison G. Abraham,[2,4] Jessica Castilho,[5] Angela Cescon,[6] Gypsyamber D'Souza,[2] Robert Dubrow,[7] Joseph J. Eron,[8] Kelly Gebo,[9] M. John Gill,[10] James J. Goedert,[1] Surbhi Grover,[11] Nancy A. Hessol,[12] Amy Justice,[13] Mari Kitahata,[14] Angel Mayor,[15] Richard D. Moore,[9] Sonia Napravnik,[8] Richard M. Novak,[16] Jennifer E. Thorne,[9] Michael J. Silverberg,[17] and Eric A. Engels[1]; for the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of the International Epidemiologic Databases to Evaluate AIDS (IeDEA)

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, and [2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [3]Department of Medicine, Division of Infectious Diseases, Center for Global Health, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; [4]Department of Ophthalmology, Johns Hopkins School of Medicine, Baltimore, Maryland; [5]Division of Infectious Diseases, Vanderbilt University Medical Center, Nashville, Tennessee; [6]Northern Ontario School of Medicine, Sudbury, Ontario, Canada; [7]Department of Epidemiology, Yale School of Public Health, New Haven, Connecticut; [8]Department of Medicine, University of North Carolina at Chapel Hill; [9]Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland; [10]Department of Medicine, University of Calgary, Alberta, Canada; [11]Department of Radiation Oncology, University of Pennsylvania, Philadelphia; [12]School of Pharmacy, University of California, San Francisco; [13]Department of Medicine, Yale School of Medicine, New Haven, Connecticut; [14]Center for AIDS Research, University of Washington, Seattle; [15]School of Medicine, Universidad Central del Caribe, Bayamon, Puerto Rico; [16]Division of Infectious Diseases, University of Illinois College of Medicine, Chicago; and [17]Division of Research, Kaiser Permanente Northern California, Oakland

Background. It is unclear whether immunosuppression leads to younger ages at cancer diagnosis among people living with human immunodeficiency virus (PLWH). A previous study found that most cancers are not diagnosed at a younger age in people with AIDS, with the exception of anal and lung cancers. This study extends prior work to include all PLWH and examines associations between AIDS, CD4 count, and age at cancer diagnosis.

Methods. We compared the median age at cancer diagnosis between PLWH in the North American AIDS Cohort Collaboration on Research and Design and the general population using data from the Surveillance, Epidemiology and End Results Program. We used statistical weights to adjust for population differences. We also compared median age at cancer diagnosis by AIDS status and CD4 count.

Results. After adjusting for population differences, younger ages at diagnosis ($P < .05$) were observed for PLWH compared with the general population for lung (difference in medians = 4 years), anal (difference = 4), oral cavity/pharynx (difference = 2), and kidney cancers (difference = 2) and myeloma (difference = 4). Among PLWH, having an AIDS-defining event was associated with a younger age at myeloma diagnosis (difference = 4; $P = .01$), and CD4 count <200 cells/μL (vs ≥500) was associated with a younger age at lung cancer diagnosis (difference = 4; $P = .006$).

Conclusions. Among PLWH, most cancers are not diagnosed at younger ages. However, this study strengthens evidence that lung cancer, anal cancer, and myeloma are diagnosed at modestly younger ages, and also shows younger ages at diagnosis of oral cavity/pharynx and kidney cancers, possibly reflecting accelerated cancer progression, etiologic heterogeneity, or risk factor exposure in PLWH.

Keywords. HIV; cancer; immunosuppression; AIDS; aging.

People living with human immunodeficiency virus (PLWH) are at increased risk of several cancer types, including those considered to be AIDS-defining events (ie, Kaposi sarcoma, certain non-Hodgkin lymphomas, and invasive cervical cancer), as well other types of cancer, particularly anal, lung, and liver cancers, and Hodgkin lymphoma [1]. Effective antiretroviral therapy (ART) has decreased AIDS-defining cancer rates and increased survival of PLWH [2]. The longevity afforded by ART

has resulted in an increased burden of non-AIDS-defining cancers over time [3, 4].

Some reports have noted that the age at cancer diagnosis is 10–20 years younger among PLWH compared with the general population across a number of cancers [5–10]. However, the proportion of PLWH who are middle-aged or older (ie, age groups at greatest cancer risk) is far smaller than in the general US population (eg, 4.0% vs 13.0% aged ≥65 years in 2010) [11, 12]. Apparent earlier ages at non-AIDS-defining cancer diagnosis in persons with AIDS are primarily explained by differences in the underlying populations at risk [13], with no evidence of a general acceleration of cancer development. However, modest but statistically significantly younger ages at lung and anal cancer diagnosis, and older ages at Hodgkin lymphoma diagnosis compared with the general population, have been reported

[13]. As this prior study was limited to people with AIDS (ie, advanced HIV disease), more studies are needed to characterize the age at cancer diagnosis in all PLWH, and to assess whether immunosuppression plays a role in accelerated cancer development as evidenced by younger ages at diagnosis.

In this study, we sought to confirm previous findings in a different study population and further explore the influence of immunosuppression on age at cancer diagnosis among all PLWH. We utilized data from 88 018 PLHW in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), which includes people at all stages of HIV infection with CD4 cell counts longitudinally measured. We compared age at cancer diagnosis between PLWH and the general population, accounting for differences in the underlying populations, and then compared age at diagnosis among PLWH by AIDS status and CD4 count.

METHODS

NA-ACCORD, a multisite consortium of clinical and interval cohorts in the United States and Canada [14], is the North American region of the International Epidemiologic Databases to Evaluate AIDS (IeDEA) initiative. Cohorts submit demographic and clinical data on PLWH (≥18 years old) using standardized data collection methods. NA-ACCORD was approved by institutional review boards at each contributing site. The current analysis included PLWH in 16 participating cohorts during 1996–2008 (Supplementary Table 1). Person-time for ages <20 and ≥80 years was excluded due to sparse data. As only birth year is collected, all birth dates were assigned as 1 July.

Cancer Diagnoses in NA-ACCORD and the General Population

Analysis of age at cancer diagnosis was restricted to the 13 most common non-AIDS-defining cancers (Table 2). Analysis of melanoma was restricted to white individuals, and breast and prostate cancers were restricted to women and men, respectively. In a subanalysis, oral cavity/pharynx cancer was further divided into sites most likely to be human papillomavirus (HPV) related and HPV unrelated [15]. Individual cohorts validated cancer diagnoses through medical records, pathology reports, or linkage with cancer registries [16]. For each cancer site, PLWH contributed person-time from the latter of 1 January 1996 or enrollment into NA-ACCORD until the first of cancer diagnosis, death, or 31 December 2008. Only the first primary cancer diagnosis of each type was considered.

AIDS onset was defined based on clinical criteria (ie, did not include CD4 counts <200 cells/μL without an AIDS-defining illness) [17]. CD4 cell counts were assigned as the measurement prior to cancer diagnosis.

Cancer data for the general population were derived from 13 population-based cancer registries in the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program during 1996–2008. Cancer sites were defined according to the *International Classification of Diseases for Oncology*, Third Edition [18].

Statistical Analysis

Initially, the unadjusted median age at diagnosis for each cancer site was compared between PLWH (NA-ACCORD) and the general population (SEER). Weights were then computed to weight the SEER population to mirror the characteristics of the NA-ACCORD population. Specifically, weights for the SEER population were computed as (person-years in NA-ACCORD/person-years in SEER), in strata defined by single year of age, race (white/non-white), and calendar time (1996–1999, 2000–2003, 2004–2008). The weights were then standardized to the total number of cancer cases in the SEER population. We then calculated the weighted median age at diagnosis in the general population and compared it to the observed ages in PLWH in NA-ACCORD using a Mood test with weights implemented in "survey" package in R [19]. A sensitivity analysis was restricted to men, as data were sparse for women.

Additionally, standardized incidence ratios (SIRs) were estimated across 10-year age groups to show the relative risk of cancer in PLWH compared to the general population. SIRs compare numbers of cancer cases observed in PLWH with expected cases, calculated by applying SEER cancer rates to the HIV population (ie, person-years) stratified by age (5-year categories), sex, race, and calendar year. A younger median age at diagnosis in PLWH would correspond with SIRs that are higher at younger ages. A *P* value for ordinal trend in SIRs across ages was estimated with Poisson regression.

For cancers that occurred at significantly younger ages among PLWH in weighted analyses, median ages at diagnosis among PLWH were compared by AIDS and recent CD4 count (<200, 200–499, ≥500 cells/μL). Each stratum was weighted to the entire NA-ACCORD population using the same weighting approach described above. Therefore, each weighted group had the same distribution of age, race, and calendar period as the full NA-ACCORD population. Analyses were carried out using SAS version 9.3 (SAS Institute, Cary, North Carolina) and R version 3.1.2 (R Project, Vienna, Austria).

RESULTS

Characteristics of 88 018 PLWH in NA-ACCORD who contributed to this analysis are presented in Table 1. In brief, 86% of the person-time was contributed by men, 45% by whites, and 41% by blacks. The most common specified HIV transmission risk group was injection drug users (28% of person-time), but a sizeable proportion had unknown HIV risk factors (37%). Most person-time was among those without AIDS (75%) and those on ART (75%). Twenty-five percent of person-time was contributed by PLWH with a CD4 count ≥500 cells/μL, 31% with a CD4 count of 200–499 cells/μL, and 15% with a CD4 count <200 cells/μL; however, 30% of person-time had missing

measurements. Among PLWH, 22% of the person-time was contributed by 20- to 39-year-olds, 67% by 40- to 59-year-olds, and 11% by 60- to 79-year-olds, whereas the corresponding proportions in the general population were 45%, 39%, and 18% (Figure 1).

In unadjusted analyses, PLWH were 7 years older at Hodgkin lymphoma diagnosis than the general population (*P* < .0001; Table 2), but the median age at diagnosis for all other cancer sites was substantially younger among PLWH (age difference: 6–14 years; all *P* < .0001).

Table 1. Characteristics of HIV-Infected Participants in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), 1996–2008

Characteristic	Person-years of Follow-up, No. (%)
Sex	
Male	419 557 (85.8)
Female	69 687 (14.2)
Age, y	
20–29	21 992 (4.5)
30–39	110 278 (22.5)
40–49	189 496 (38.7)
50–59	125 302 (25.6)
60–69	33 382 (6.8)
70–79	8793 (1.8)
Race	
White	218 980 (44.8)
Black	199 809 (40.8)
Other/unknown	70 455 (14.4)
Risk group	
MSM	110 505 (22.6)
IDU	136 233 (27.8)
Heterosexual	57 625 (11.8)
Other	6493 (1.3)
Unknown[a]	178 388 (36.5)
Calendar period	
1996–1999	88 680 (18.1)
2000–2003	163 830 (33.5)
2004–2008	236 734 (48.4)
AIDS status	
No	365 853 (74.8)
Yes	123 391 (25.2)
Ever ART use	
No	121 008 (24.7)
Yes	368 235 (75.3)
CD4 cell count, cells/μL	
Missing[b]	146 019 (29.8)
<200	71 784 (14.7)
200–499	150 447 (30.8)
≥500	120 934 (24.7)

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IDU, injection drug user; MSM, men who have sex with men; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design.

[a]A large fraction of the data in the unknown risk group category come from a single NA-ACCORD cohort, the Veterans Aging Cohort Study and Virtual Cohort, which does not collect risk group.

[b]CD4 cell counts were ascertained in each calendar year. If CD4 counts were missing, values were carried forward from the prior year; if no value was available then CD4 counts were set to missing for that interval.

After weighting the general population to have the identical distribution of age, race and calendar period as NA-ACCORD, there was no statistically significant difference in median age at diagnosis for 8 cancer types. Small but statistically significantly younger ages at diagnosis were observed for PLWH compared with the general population for lung (median, 54 vs 58 years), anal (47 vs 51), oral cavity/pharynx (51 vs 53), and kidney cancers (52 vs 54) and myeloma (52 vs 56; all *P* < .05). A 1-year difference was observed for both HPV-related (52 vs 53 years; *P* = .03) and HPV-unrelated (51 vs 52; *P* = .14) oral cavity/pharynx cancer sites. A sensitivity analysis restricted to men was consistent with the overall results, with the exception of a significantly younger median age at melanoma diagnosis (49 vs 54 years; *P* = .0009).

Overall SIRs were significantly elevated for lung (SIR, 2.21; 95% confidence interval [CI], 2.04–2.38), anal (SIR, 32.0; 95% CI, 28.4–35.9), and oral cavity/pharynx cancer (SIR, 1.90; 95% CI, 1.63–2.21) and myeloma (SIR, 1.35; 95% CI, 1.00–1.79), but not kidney cancer (SIR, 1.16; 95% CI, .96–1.40). The SIRs declined significantly with increasing age for each of these cancers (all *P* for trend < .05), indicating that cancer risk in PLWH was more strongly elevated at younger ages (Figure 2). There were significant elevations across all ages for lung, anal, and oral cavity/pharynx cancers, with the exception of 70- to 79-year-olds for lung and oral cavity/pharynx cancers. In contrast, SIRs for kidney cancer were not elevated or only somewhat elevated for 30- to 39-, 40- to 49-, and 50- to 59-year-olds and reduced among 60- to 69- and 70- to 79-year-olds. Myeloma risk was only increased among 30- to 39-year-olds.

After standardization to the entire NA-ACCORD, the age at diagnosis was significantly younger among people with AIDS compared with people with HIV for myeloma only (50 vs 54; *P* = .01; Figure 3), and a CD4 count <200 cells/μL was associated with a significantly younger median age at diagnosis for lung cancer only (vs 200–499 cells/μL: 51 vs 55, *P* = .008; ≥500 cells/ μL: 51 vs 55, *P* = .006).

DISCUSSION

Using data from the largest consortium of HIV cohorts in North America, we showed there is not a broad acceleration in the development of cancer among PLWH manifesting as younger ages at cancer diagnosis across cancer types. Nonetheless, after adjustment for population differences in age, race, and calendar period, PLWH were diagnosed with lung, anal, oral cavity/pharynx, and kidney cancers and myeloma at modestly younger ages than the general population. Further, among PLWH, the median age at myeloma diagnosis was younger among people with AIDS and the median age at lung cancer diagnosis was younger among people with CD4 counts <200 cells/μL, suggesting a potential role of more profound immunosuppression in the accelerated development of these cancers.
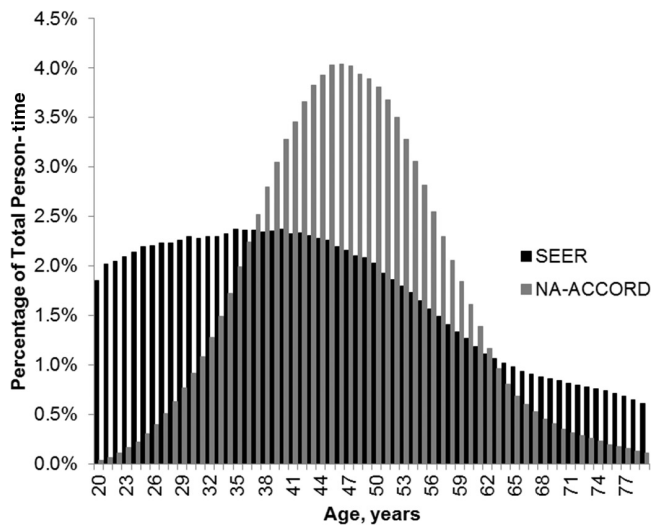
Figure 1. Fraction of total person-time in the human immunodeficiency virus (HIV)-infected population (North American AIDS Cohort Collaboration on Research and Design [NA-ACCORD]) and the general population (Surveillance Epidemiology and End Results [SEER-13]) by single year of age, 1996–2008. Person-time in the HIV-infected population (NA-ACCORD, gray bars) and the general population (SEER-13, black bars). Bars represent the fraction of person-time contributed by each single year of age from 20 to 79 years old.

As in previous work, large apparent differences in age at diagnosis for many cancers were driven by dramatic differences in the underlying age distributions of the HIV-infected and general populations [13]. Although more PLWH are living to older ages, at present only 4% of the US HIV population is ≥65 years old, compared with 13% in the general population [11, 12]. Similarly, only 5% of PLWH in the

Canadian Observational Cohort Collaboration are ≥65 years old (Cescon, unpublished data) compared with 15% in the Canadian general population [20]. This smaller fraction of PLHW at older ages, when cancer risk is greatest, inherently drives down the age at cancer diagnosis relative to the general population. To compare median ages at cancer diagnosis in an unbiased way, the HIV and general populations must be matched or standardized to have an identical underlying age distribution [13, 21–23]. An analogous approach is to compare SIRs across age groups, with younger ages at diagnosis manifesting as higher SIRs at younger ages.

This study confirmed prior findings of modest, but statistically significant, younger ages at diagnosis of lung cancer, anal cancer, and myeloma among PLWH [13]. Using a different methodology from the current study, researchers previously reported similar small, but significant, younger ages at diagnosis for lung and anal cancer among PLWH in the Kaiser Permanente HIV cohort [22] compared with matched HIV-uninfected controls. A study using the French Hospital Database on HIV observed modestly younger ages at diagnosis for lung, but not anal cancer [23]. Although in a prior study the younger age at myeloma diagnosis was not significant after correction for multiple comparisons, the *P* value was strong (*P* = .004) [13], and considered together with the current study we believe there is compelling evidence for replication. In contrast to prior findings [13], median age at Hodgkin lymphoma diagnosis was not older among PLWH.

Evidence was less clear for several other cancers. Median ages at oral cavity/pharynx and kidney cancer diagnosis were

Table 2. Comparison of Median Ages at Diagnosis Between HIV-Infected People in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) and the General Population, After Weighting the General Population to the Age Structure of NA-ACCORD

Cancer	Observed in HIV-Infected Individuals		Observed in General Population	General Population After Weighting[a]	
	Cases	Median Age, y	Median Age, y	Median Age, y	*P* Value
Lung	644	54	68	58	<.0001
Prostate	504	58	66	59	.43
Anus	291	47	57	51	<.0001
Liver	226	54	62	54	.50
Oral cavity and pharynx	173	51	60	53	.04
Hodgkin lymphoma	171	44	39	45	.98
Colon	111	55	67	56	.55
Kidney	109	52	62	54	.0003
Larynx	86	53	63	56	.09
Melanoma (whites only)	77	49	56	51	.18
Breast	56	48	58	47	.27
Pancreas	55	53.5	67	57	.14
Myeloma	49	52	66	56	.008

Abbreviations: HIV, human immunodeficiency virus; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design.

[a]The Surveillance Epidemiology and End Results (SEER) population was weighted to NA-ACCORD population in strata defined by single year of age, calendar period, and race. The *P* value compares the ages in the general population after weighting to the observed ages in HIV-infected individuals in NA-ACCORD.
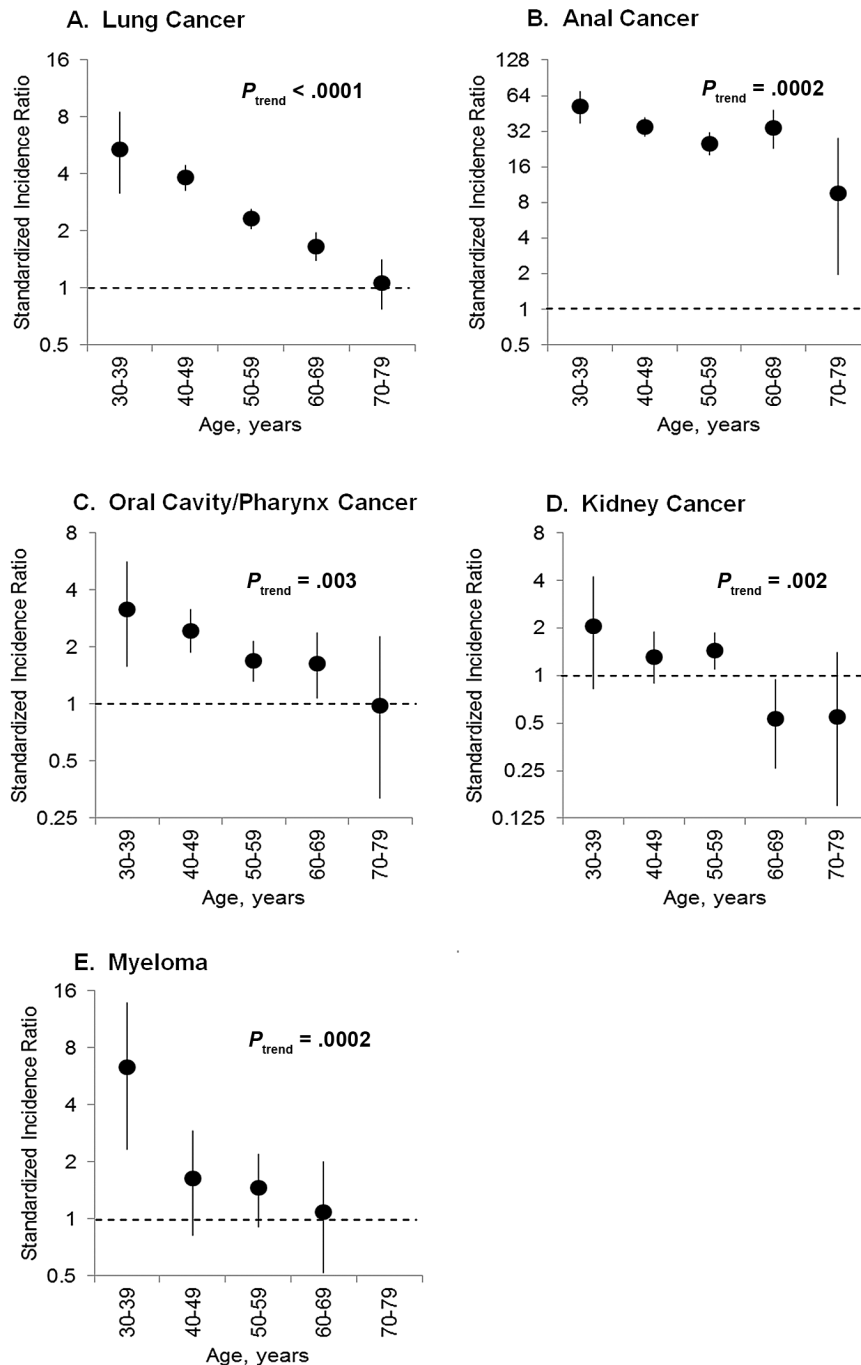
Figure 2. Standardized incidence ratios (SIRs) comparing cancer risk in human immunodeficiency virus-infected people to the general population across age groups for lung cancer (*A*), anal cancer (*B*), oral cavity and pharynx cancers (*C*), kidney cancer (*D*), and myeloma (*E*). Points represent SIRs and lines represent 95% confidence intervals (CIs). SIRs were standardized by age, sex, race, and calendar period. No point is presented for 70- to 79-year-olds in the myeloma figure, as there were no observed cases (SIR, 0 [95% CI, 0–.88]).

2 years younger in PLHW, but the evidence for these cancers is weaker, as significant differences were not seen in prior work (*P* = .40 and .17, respectively) [13]. Further, SIRs for kidney cancer were not elevated in any age group, arguing against a biological effect of HIV. Melanoma showed some evidence of younger age at diagnosis among men only, but this was not observed overall or in a previous study [13].

One possible explanation for modestly younger ages at diagnosis for certain cancers in PLWH is that HIV disease may slightly accelerate time from the initiation of the carcinogenic process to clinical disease due to biological effects of immunosuppression, immune activation, and inflammation. Unlike a prior study that was limited to people with AIDS, the present study could assess the association between
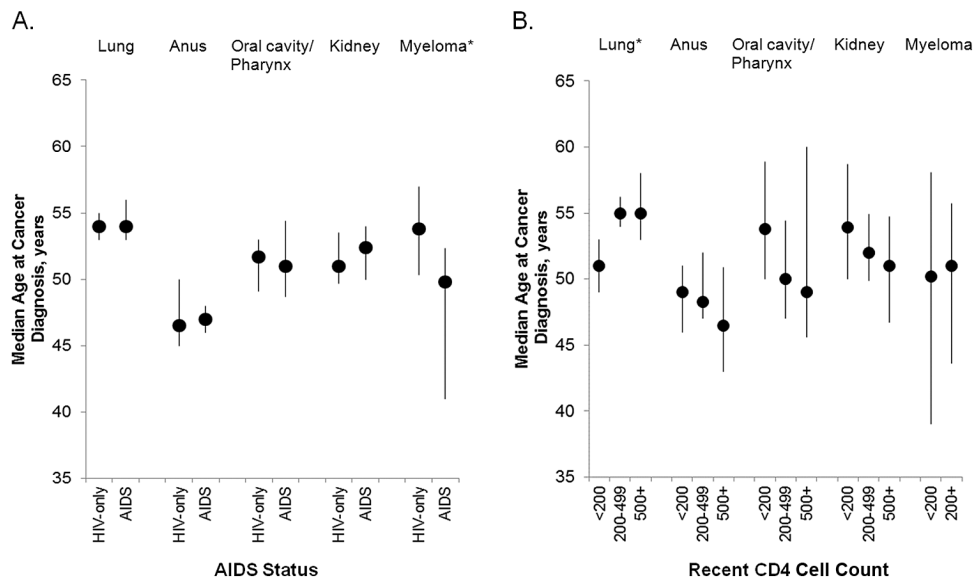
Figure 3. Median age at cancer diagnosis by AIDS status (*A*) and CD4 cell counts (*B*) for lung cancer, anal cancer, oral cavity and pharynx cancers, kidney cancer, and myeloma in human immunodeficiency virus (HIV)-infected people. Points represent median ages at diagnosis and lines represent 95% confidence intervals (CIs). Asterisks indicate statistically significant differences in weighted median ages (p<0.05). All estimates were standardized to the full North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) population by single year of age, race, and calendar period. The adjusted median ages at diagnosis for people living with HIV with a missing CD4 cell count were 44 years (95% CI, 43–46) for anal cancer, 50 years (95% CI, 46.5–53.0) for kidney cancer, 54 years (95% CI, 53–55.2) for lung cancer, 53 years (95% CI, 49.2–57.5) for myeloma, and 51 years (95% CI, 48.4–53) for oral cavity/pharynx cancer.

immunosuppression and age at cancer diagnosis by examining AIDS status and CD4 count. Myeloma was diagnosed at younger ages among people with AIDS, and lung cancer was diagnosed at younger ages among people with current CD4 counts <200 cells/μL. For lung cancer and myeloma, the inconsistent associations of age at diagnosis with CD4 count, a marker of current immune status, and prior AIDS status, which captures whether a person ever previously had severe immunosuppression, may reflect differences in the timing of immunosuppression in relation to the accelerated progression of these cancers.

Younger ages at cancer diagnosis may also be due to earlier or more intense exposure to key risk factors in PLWH [24]. For example, the prevalence of current smoking is 54% in PLWH overall and 74% among injection drug users, compared with 20% in the general population [24]. Furthermore, HIV infection is associated with a higher prevalence and persistence of high-risk anal HPV infections among men who have sex with men (MSM), the risk group with the highest anal cancer risk [25]. As lung and anal cancers are primarily caused by cigarette smoking [26] and high-risk HPV infections [27], respectively, it is possible that earlier or more intense exposure to cigarette smoking and anal HPV could result in younger ages at cancer diagnosis. Of note, cigarette smoking also causes oral cavity/pharynx and kidney cancers [26], and HIV is associated with a higher prevalence of high-risk oral HPV infections, which cause certain oropharynx cancers [24, 27]. Earlier and/or greater exposure to

risk factors may also contribute to an accelerated development of these cancers.

Etiologic heterogeneity may play a role in the younger age at myeloma diagnosis among PLWH. Myeloma risk was increased only among younger PLWH. A similar finding was observed among solid organ transplant recipients, another immunosuppressed population [28]. One possibility is that immunosuppression may increase the risk of rare Epstein-Barr (EBV)–positive myelomas, which may have a younger age at onset [28]. If HIV increases the risk of EBV-positive earlier-onset myeloma, but does not affect the risk of the more common EBV-negative myeloma cases that typically occur at older ages, a shift to younger ages at myeloma diagnosis would occur among PLWH.

Cancer may be diagnosed at somewhat younger ages due to increased cancer screening or surveillance among PLWH who regularly access medical care. This is not a general phenomenon, as screen-detectable cancers such as breast, prostate, and colon cancers were not diagnosed at younger ages, but it is possible that our anal cancer finding was driven by an increased prevalence of anal Pap testing in PLWH, particularly MSM [29]. In contrast, lung cancers are diagnosed at somewhat later stages in PLWH [30], potentially reflecting delayed detection, and there is no population-wide screening program for myeloma, kidney cancer, or oral cavity/pharynx cancer.

Finally, the competing risk of death due to AIDS and other causes may contribute to younger ages at diagnosis. If cancer

and death risk among PLWH are not independent, cancer incidence may be reduced at older ages, which would lead to a younger age at diagnosis among observed cases. Although we did not account for competing risks in our analysis, the lack of younger ages across sites argues against a widespread effect.

The main strength of this analysis was the use of a large consortium of HIV cohorts that included people with and without AIDS, and availability of CD4 counts. In addition, we used weighted analyses, correcting the bias induced by comparing ages at diagnosis across populations with different distributions of age and other characteristics. The main limitation is the lack of information on important cancer risk factors, including detailed information on smoking and anal HPV infection. Furthermore, although most study participants had CD4 cell count data while under study, a large fraction of cases were missing prior CD4 cell counts. Additionally, SEER data may not be representative of the entire US or Canadian population. While our overall findings largely replicate prior results [13], some associations (particularly for subgroups) could be the result of chance given multiple comparisons. It is important to note that the age at diagnosis is just one metric for comparing cancers in PLWH and the general population. Although it is an easily understood summary measure, it masks relevant information on whether cancer risk is elevated and informative patterns in rates across age groups.

Efforts to reduce cancer risk in PLWH are needed to prevent many cancer types, regardless of whether age at diagnosis is younger. Cancer prevention and early detection is particularly important as the number of older PLWH continues to grow [4]. These cancer prevention efforts include appropriate initiation of ART to prevent AIDS-defining cancers and other immunosuppression-related cancers, facilitation of smoking cessation, and detection and treatment of hepatitis B and C viruses. Furthermore, PLWH should receive age-appropriate cancer screening based on general population guidelines. More research is needed on screening for lung and anal cancers among PLWH. There are no national screening guidelines for anal cancer [31]. The ongoing Anal Cancer/HSIL Outcomes Research (ANCHOR) Study is examining the benefits of treating precancerous anal lesions in PLWH that may be detected through screening (National Institutes of Health clinical trials identification number: NCT02135419). Low-dose computed tomography (LDCT) is recommended for the early detection of lung cancer for some current and former smokers [32]; however, more data are needed on the sensitivity and specificity of LDCT among PLWH.

In summary, although we have confirmed prior findings that 3 malignancies (anal cancer, lung cancer, and myeloma) develop 3–4 years earlier than in the general population, the development of other cancers does not seem to be broadly accelerated in PLWH. Additionally, there is some evidence that immunosuppression is associated with younger ages at lung cancer and myeloma diagnoses. Although there is not a general acceleration of cancer development in PLWH, the cancer burden will continue to grow as the population ages, highlighting the need for cancer prevention and early detection.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

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APPENDIX