IDSA
Infectious Diseases Society of America

hivma
hiv medicine association

OXFORD

Cancer Risk in Older Persons Living With Human Immunodeficiency Virus Infection in the United States

Parag Mahale,[1] Eric A. Engels,[1] Anna E. Coghill,[1] Amy R. Kahn,[2] and Meredith S. Shiels[1]

[1]Division of Cancer Epidemiology & Genetics, National Cancer Institute, Rockville, Maryland, and [2]New York State Cancer Registry, New York State Department of Health, Albany

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

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

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

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

Keywords. HIV; cancer; aging; epidemiology.

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

The introduction of highly active antiretroviral therapy (HAART) has led to a steady increase in the life expectancy of PLWH [11]. Consequently, the number of older PLWH in the United States has also increased. In 2014, approximately 44% of PLWH in the United States were aged ≥50 years, and 17% of new HIV diagnoses were made in this age group [12, 13]. Because of improved immunity due to HAART, rates of ADCs have declined

over the past 2 decades [7, 14, 15]. However, rates of many NADCs increase with age. It is unclear whether age-related immune senescence in the setting of HIV-related immunosuppression will result in particularly elevated cancer rates among older PLWH.

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

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

SUBJECTS AND METHODS

Study Population and Outcomes

The US HIV/AIDS Cancer Match study links data from population-based HIV and cancer registries using a probabilistic algorithm (https://hivmatch.cancer.gov) [14]. This analysis

included data from 9 US states/territories (see footnote to Table 1). This study was approved by the institutional review boards at the National Cancer Institute and, as required, by participating cancer and HIV registries.

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

We evaluated the risks of ADCs—KS, cervical cancer, and NHL (overall and by subtypes: diffuse large B-cell lymphoma, Burkitt lymphoma, primary central nervous system [CNS] lymphoma, and other/unspecified NHLs)—and certain NADCs with increased incidence among PLWH: cancers of the anus, lung, liver, and oral cavity/pharynx and Hodgkin lymphoma [5]. Female breast, colon, and prostate cancers were also included; although their rates increase with age, they are not elevated among PLWH [5]. The remaining cancers were grouped together in a separate category. Cancers were classified using the *International Classification of Diseases for Oncology* (third edition) topography and morphology codes for invasive cancers (Supplementary Table S1) [20].

Statistical Analyses

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

Among PLWH, we estimated cancer risk according to age (50–59, 60–69, or ≥70 years), AIDS diagnosis (yes or no), and time since HIV diagnosis (≤5, 5.01–10, 10.01–15, or ≥15.01 years) by fitting Poisson regression models for each cancer type. Adjusted

Table 1. Person-Years Contributed by Older Persons Living With Human Immunodeficiency Virus Infection According to Age Categories[a]

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

Abbreviations: HIV, human immunodeficiency virus; IDUs, injection drug users; MSM, men who have sex with men; PY, person-years.

[a]Participating registries included the following: Colorado (years of coverage, 1996–2007), Connecticut (2005–2010), Georgia (2004–2012), Maryland (2008–2012), Michigan (1996–2010), New Jersey (1996–2012), New York (2001–2012), Puerto Rico (2003–2012), and Texas (1999–2009).

incidence rate ratios (aIRRs) were adjusted for race/ethnicity, sex/risk group, calendar year, region, prior AIDS diagnosis, and time since HIV diagnosis (in models for age) or age (in models for time since HIV diagnosis). Age, calendar year, prior AIDS diagnosis, and time since HIV diagnosis variables were updated over time.

We conducted some sensitivity analyses. Because outmigration of persons from registry areas may result in overestimating the person-time at risk, we decreased the person-time by 10% for PLWH after 10 years of follow-up and recalculated the SIRs [22]. It is possible that more cancer cases may be diagnosed shortly after HIV infection because there may be a period of increased medical care around that time. Hence, we excluded the first year after HIV diagnosis date and reestimated cancer risk according to time since HIV diagnosis. Because the risk of ADCs and NADCs have changed since the introduction of HAART, we restricted the follow-up time to calendar years 2001–2012 and recalculated the SIRs and aIRRs. Finally, we evaluated whether associations between age and cancer risk differed by time since HIV diagnosis, and whether associations between time since HIV diagnosis and cancer risk differed by age.

RESULTS

We studied 183 542 PLWH aged ≥50 years old who contributed 928 194 person-years of follow-up (Table 1). The person-time distribution was 75.1% in 50–59-year-olds, 20.4% in 60–69-year-olds, and 4.5% in those aged ≥70 years. A large fraction of person-time was contributed by non-Hispanic blacks (47.6%), men (74.3%), and those with a prior AIDS diagnosis (71.9%). A large proportion of person-time for the time since

HIV diagnosis was unknown (22.2%). Among PLWH with a known date of HIV diagnosis, >60% were infected with HIV for ≥5 years, and approximately 20% had been living with HIV infection for >15 years.

During the follow-up, 10 371 cancers were diagnosed, of which 1647 (15.9%) were ADCs and 8724 (84.1%) were NADCs (Table 2). As expected, rates were increased in older PLWH compared with the general population for KS (SIR, 103.34), total NHL (3.05), and cervical cancer (2.02). Among NHLs, rates were strongly elevated for CNS lymphoma (SIR, 47.39) and Burkitt lymphoma (13.75). Among the NADCs, a very high risk of anal cancer (SIR, 14.00) was observed, followed by Hodgkin lymphoma (7.61). Rates were moderately increased for liver (SIR, 2.91), lung (1.71), and oral cavity/pharyngeal cancers (1.66). Furthermore, rates of breast (SIR, 0.61), prostate (0.47), and colon cancer (0.63) were significantly lower among PLWH than in the general population. The SIRs did not differ appreciably after the person-time was adjusted for late follow-up, or when analyses were restricted to calendar years 2001–2012 (Supplementary Tables S2 and S4).

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

Examining cancer incidence rates among PLWH by age group (Table 3), we observed a significant decrease in KS risk

Table 2. Rates and Standardized Incidence Ratios of Cancers in Older Persons Living With Human Immunodeficiency Virus Infection (Age ≥50 Years)

Cancers	Observed Cases, No.	Expected Cases, No.	IR per 100 000 PY	SIR (95% CI)
All cancers	10371	8929	1117.3	1.16 (1.14–1.18)
ADCs				
Kaposi sarcoma	338	3.3	36.4	103.34 (92.62–114.97)
NHL	1222	401.2	131.7	3.05 (2.88–3.22)
Diffuse large B cell	674	110.0	72.6	6.12 (5.67–6.61)
Burkitt	103	7.5	11.1	13.75 (11.23–16.68)
CNS	74	8.1	8.0	47.39 (37.21–59.49)
Other/unspecified	371	282.1	39.9	1.32 (1.18–1.46)
Cervical cancer	87	43.0	36.5	2.02(1.62–2.49)
NADCs				
Anal	524	37.4	56.5	14.00 (12.82–15.25)
Lung	1725	1012	185.8	1.71 (1.63–1.79)
Liver	805	276.4	86.7	2.91 (2.71–3.12)
Hodgkin lymphoma	253	33.3	27.3	7.61 (6.70–8.60)
Oral cavity/pharynx	461	278.4	49.7	1.66 (1.51–1.81)
Female breast	329	542.0	137.9	0.61 (.54–.68)
Prostate	1341	2829	194.5	0.47 (.45–.50)
Colon (excluding rectum)	360	571.3	38.8	0.63 (.57–.70)
Other cancers	2926	5731	315.2	1.01 (.97–1.05)

Abbreviations: ADCs, AIDS-defining cancers; CI, confidence intervals; CNS, central nervous system; IR, incidence rate; NADCs, non–AIDS-defining cancers; NHL, non-Hodgkin lymphoma; PY, person-years; SIR, standardized incidence ratio.
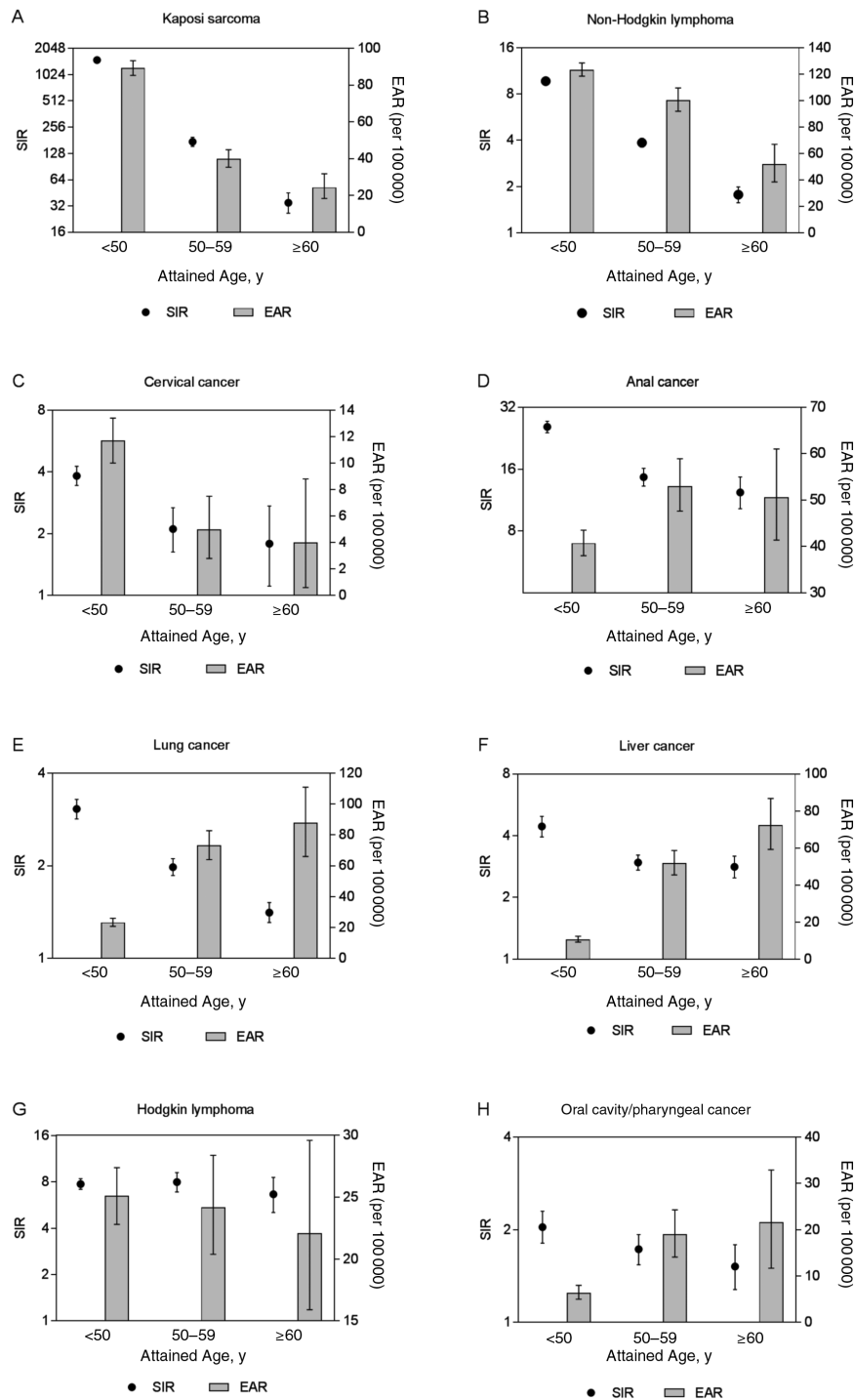
Figure 1. Risk of cancers in persons living with human immunodeficiency virus (HIV) compared with the general population. The figure plots the standardized incidence ratios (SIRs) on the left y-axis, the excess absolute risks (EARs) per 100 000 population on the right y-axis, and 3 age groups on the x-axis (<50, 50–59, and ≥60 years). *A–C*, Risks of 3 AIDS-defining cancers: Kaposi sarcoma (*A*), non-Hodgkin lymphoma (*B*), and cervical cancer (*C*). *D–H*, Risks of 5 non-AIDS-defining cancers: anal cancer (*D*), lung cancer (*E*), liver cancer (*F*), Hodgkin lymphoma (*G*), and oral cavity/pharynx cancer (*H*).

with increasing age. Compared with 50–59-year-olds, PLWH aged 60–69 (aIRR, 0.68) or ≥70 (0.43) years had lower KS rates (P_{trend} = .001). In contrast, rates for lung, prostate, and colon cancers increased with age (P_{trend} < .001) while the increasing trend for breast cancer was borderline significant (P_{trend} = .058). Liver and oral cavity/pharyngeal cancer rates were higher among 60–69-year-olds than in the 50–59-year age group (P_{trend} < .05). No association between age and cancer risk was observed for NHL (total or subtypes), cervical cancer, anal cancer, or Hodgkin lymphoma (P_{trend} > .05).

Table 3. Risk of Cancers in Older Persons Living With Human Immunodeficiency Virus Infection According to Age and Prior AIDS Diagnosis

Cancers	Age 50–59 y		Age 60–69 y		Age ≥70 y		P_{trend}	AIDS Diagnosis (Yes vs No): aIRR[b] (95% CI)
	Cancers, No.	aIRR[a] (95% CI)	Cancers, No.	aIRR[a] (95% CI)	Cancers, No.	aIRR[a] (95% CI)		
ADCs								
Kaposi sarcoma	280	Reference	51	0.68 (.51–.92)	7	0.43 (.20–.92)	.001	1.86 (1.40–2.47)
NHL	946	Reference	227	0.90 (.78–1.04)	49	0.88 (.66–1.18)	.13	1.74 (1.50–2.01)
Diffuse large B cell	521	Reference	127	0.90 (.74–1.10)	26	0.84 (.56–1.25)	.21	1.97 (1.61–2.41)
Burkitt[c]	82	Reference	21	0.80 (.49–1.30)	…	…	.37	1.22 (.77–1.92)
CNS[c]	63	Reference	11	0.53 (.28–1.01)	…	…	.053	5.17 (2.25–12.21)
Other/unspecified	280	Reference	71	0.94 (.73–1.21)	20	1.12 (.71–1.77)	.33	1.50 (1.18–1.90)
Cervical cancer[c]	66	Reference	21	1.10 (.67–1.82)	…	…	.70	1.50 (.91–2.49)
NADCs								
Anal	397	Reference	112	1.05 (.85–1.29)	15	0.66 (.40–1.11)	.45	2.66 (2.04–3.47)
Lung	1030	Reference	552	2.11 (1.90–2.34)	143	2.62 (2.20–3.13)	<.001	1.37 (1.22–1.53)
Liver	546	Reference	226	1.61 (1.38–1.89)	33	1.29 (.91–1.84)	<.001	0.92 (.78–1.09)
Hodgkin lymphoma	193	Reference	53	1.00 (.74–1.36)	7	0.58 (.27–1.23)	.32	2.19 (1.55–3.09)
Oral cavity/pharynx	315	Reference	132	1.55 (1.26–1.90)	14	0.76 (.44–1.30)	.03	1.67 (1.31–2.12)
Female breast	232	Reference	77	1.26 (.97–1.63)	20	1.32 (.83–2.09)	.058	1.03 (.82–1.31)
Prostate	627	Reference	550	3.11 (2.77–3.49)	164	4.12 (3.46–4.90)	<.001	0.84 (.74–.94)
Colon (excluding rectum)	177	Reference	125	2.59 (2.06–3.26)	58	5.28 (3.90–7.15)	<.001	0.89 (.71–1.13)
Other cancers	1845	Reference	829	1.69 (1.55–1.83)	252	2.34 (2.05–2.68)	<.001	1.25 (1.15–1.36)

Abbreviations: ADCs, AIDS-defining cancers; aIRR, adjusted incidence rate ratio; CI, confidence intervals; CNS, central nervous system; NADCs, non–AIDS-defining cancers; NHL, non-Hodgkin lymphoma.

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

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

[c]aIRRs and P_{trend} values for these cancers are presented for the 50–59- and ≥60-year age groups because too few cancers occurred in the ≥70-year category (1 Burkitt lymphoma, 2 CNS lymphomas, and 2 cervical cancers).

PLWH with a prior AIDS diagnosis had increased rates of KS, NHL (particularly diffuse large B-cell lymphoma [aIRR, 1.97] and CNS lymphomas [5.17]), anal, lung, and oral cavity/pharyngeal cancer, and Hodgkin lymphoma than those without a previous AIDS diagnosis (aIRRs range, 1.37–2.66; Table 3). Prostate cancer rates were lower among those with a prior AIDS diagnosis (aIRR, 0.84), but rates of cervical, liver, breast, and colon cancer did not differ significantly .

The risk of most cancers was highest within the first 5 years after HIV diagnosis, gradually decreasing over time (Table 4). Significant decreasing trends were observed for KS ($P_{trend} < .001$), total NHL ($P_{trend} < .001$), lung cancer ($P_{trend} < .001$), breast cancer ($P_{trend} = .02$), and Hodgkin lymphoma ($P_{trend} = .04$), with a marginally significant trend for prostate cancer ($P_{trend} = .07$). In contrast, there was an indication that risk increased with increasing time since HIV diagnosis for anal ($P_{trend} = .07$) and liver ($P_{trend} = .08$) cancers. Excluding the first year after HIV diagnosis did not affect our results (Supplementary Table S3). Restricting the analyses to calendar years 2001–2012 did not affect the associations between age or time since HIV diagnosis and cancer risk (Supplementary Tables S5 and S6).

The associations between age and cancer risk did not differ by time since HIV diagnosis for all cancers (all $P_{interaction} > .05$). However, there was significant heterogeneity in the association between time since HIV diagnosis and cancer risk by age for NHL ($P_{interaction} = .003$) and Hodgkin lymphoma ($P_{interaction} = .02$).

The aIRRs for NHL decreased with time since HIV diagnosis for both age categories ($P_{trend} < .001$ for ages 50–59 and ≥60 years). For Hodgkin lymphoma, the trend for decreasing rates with time since HIV diagnosis was observed only for ≥60-year-olds ($P_{trend} = .006$) and not among those aged 50–59 years ($P_{trend} = .41$).

DISCUSSION

With the success of HAART, HIV infection has been transformed from a terminal illness to a more manageable chronic disease. Consequently, more PLWH are reaching older ages. In our analyses that included >180 000 older PLWH, we observed that cancer risk was elevated in older PLWH compared with the general population, although the relative risk for most cancers declined with age. However, EARs, which measure absolute risk and thus reflect the number of excess cancers occurring among PLWH, increased with age for some NADCs. We also observed that for many cancers, cancer risk was highest within the first 5 years after HIV diagnosis.

In the past 20 years, there has been a steady shift in the demographic profile of the HIV/AIDS epidemic in the United States toward older age groups. In 2002, the Centers for Disease Control and Prevention estimated that approximately 8.5% of PLWH were >50 years of age, and that proportion had increased to 44% in 2014 [12]. With aging, there is a complex interaction between various biological processes which may modulate cancer risk among PLWH: (1) factors related to aging, including

Table 4. **Risk of Cancers in Older Human Immunodeficiency Virus-Infected Individuals According to Time Since Human Immunodeficiency Virus Diagnosis**

Cancers	≤5 y Since Diagnosis		5.01–10 y Since Diagnosis		10.01–15 y Since Diagnosis		≥15.01 y Since Diagnosis		P_{trend}
	Cancers, No.	aIRR[a] (95% CI)	Cancers, No.	aIRR[a] (95% CI)	Cancers, No.	aIRR[a] (95% CI)	Cancers, No.	aIRR[a] (95% CI)	
ADCs									
Kaposi sarcoma	95	Reference	81	0.58 (.43–.79)	55	0.44 (.31–.63)	40	0.43 (.29–.65)	<.001
NHL	355	Reference	308	0.60 (.51–.70)	204	0.45 (.38–.54)	123	0.36 (.29–.45)	<.001
Diffuse large B cell	183	Reference	164	0.60 (.49–.75)	122	0.50 (.39–.64)	66	0.36 (.26–.49)	<.001
Burkitt	33	Reference	22	0.44 (.25–.76)	18	0.39 (.21–.72)	9	0.24 (.11–.53)	<.001
CNS	24	Reference	19	0.54 (.29–1.00)	10	0.33 (.15–.71)	10	0.46 (.20–1.05)	.02
Other/unspecified	115	Reference	103	0.63 (.48–.82)	54	0.39 (.28–.54)	38	0.38 (.26–.55)	<.001
Cervical cancer	21	Reference	22	0.75 (.40–1.37)	16	0.61 (.31–1.23)	12	0.64 (.29–1.43)	.20
NADCs									
Anal	59	Reference	99	1.03 (.74–1.43)	140	1.50 (1.09–2.06)	95	1.21 (.86–1.72)	.07
Lung	355	Reference	459	0.92 (.80–1.06)	367	0.87 (.74–1.02)	213	0.70 (.58–.84)	<.001
Liver	98	Reference	155	0.97 (.75–1.26)	180	1.17 (.90–1.51)	157	1.20 (.91–1.59)	.08
Hodgkin lymphoma	64	Reference	61	0.69 (.48–.99)	41	0.54 (.36–.82)	39	0.70 (.45–1.09)	.04
Oral cavity/pharynx	79	Reference	117	1.02 (0.76–1.36)	96	0.93 (.68–1.27)	66	0.82 (.57–1.17)	.22
Female breast	75	Reference	90	0.85 (.62–1.17)	63	0.72 (.50–1.02)	38	0.64 (.42–.98)	.02
Prostate	231	Reference	363	1.08 (.91–1.27)	272	0.94 (.78–1.13)	191	0.86 (.70–1.07)	.07
Colon (excluding rectum)	68	Reference	90	0.94 (.68–1.30)	82	1.03 (.73–1.45)	43	0.75 (.49–1.14)	.32
Other cancers	568	Reference	741	0.91 (.82–1.02)	643	0.91 (.80–1.02)	429	0.79 (.69–.91)	<.001

Abbreviations: ADCs, AIDS-defining cancers; aIRR, adjusted incidence rate ratio; CI, confidence intervals; CNS, central nervous system; NADCs, non–AIDS-defining cancers; NHL, non-Hodgkin lymphoma.

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

age-related immune senescence; (2) factors associated with HIV infection and its related immune dysfunction, such as HIV viral load, CD4$^+$ T-cell count, and effectiveness of HAART; and (3) various host factors that may affect cancer risk, such as viral coinfections and smoking. Furthermore, the immunosuppressive state in PLWH changes over time. The natural course of HIV infection is characterized by progressive decline in immune function from primary HIV infection to symptomatic disease with onset of AIDS-defining conditions [23]. HAART alters the natural history of HIV infection with gradual improvement of immunosuppressive state and restoration of CD4$^+$ T-cell count over time. In addition, the duration of immunosuppression in a person infected with HIV also increases with time.

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

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

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

We observed lower risk of breast, prostate, and colon cancer rates in older PLWH compared with the general population, as reported elsewhere [26, 30–33]. As in the general population, prostate and colon cancer rates increased with age, and the trend for breast cancer was borderline significant. Because these are common screen-detectable cancers, it has been speculated that their reduced rates may reflect lower rates of cancer screening among PLWH compared with the general population. However, recent studies suggest that the deficit of breast, colon, and prostate cancers among PLWH cannot be completely explained by lower rates of cancer screening [34, 35]. Biological explanations for these deficits need to be explored further.

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

Strength of our study included the use of a large population-based cohort of >180 000 PLWH aged ≥50 years with systematic cancer ascertainment and the evaluation of cancer risk by time since HIV diagnosis. However, we were unable to include information on HAART use, $CD4^+$ T-cell count, or HIV viral load in our analyses. Therefore, we cannot definitively interpret trends with respect to time since HIV diagnosis. In addition, our data do not include information about cancer risk factors, such as cigarette smoking and viral coinfection. Because the timing of HIV acquisition was not known, the duration of HIV infection could be calculated only from the first available positive serological test date, and we were missing this information for 22.2% of person-time contributed by PLWH in our study. We were unable to adjust for competing risks due to coexisting comorbid conditions in our analyses. We used the general population as our control group because we did not have access to an ideal HIV-uninfected population that may have similar characteristics to PLWH [39]. Finally, our analysis includes only PLWH in whom HIV infection has been diagnosed, and an estimated 13% of PLWH are unaware that they are infected, >7% of whom may be >50 years of age [40].

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

Supplementary Data

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

Notes

References

1. Park LS, Hernández-Ramírez RU, Silverberg MJ, Crothers K, Dubrow R. Prevalence of non-HIV cancer risk factors in persons living with HIV/AIDS: a meta-analysis. AIDS 2016; 30:273–91.
2. Althoff KN, McGinnis KA, Wyatt CM, et al; Veterans Aging Cohort Study (VACS). Comparison of risk and age at diagnosis of myocardial infarction, end-stage renal disease, and non-AIDS-defining cancer in HIV-infected versus uninfected adults. Clin Infect Dis 2015; 60:627–38.
3. Clifford GM, Polesel J, Rickenbach M, et al; Swiss HIV Cohort. 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.

4. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet **2007**; 370:59–67.

5. Hernandez-Ramirez RU, Shiels MS, Dubrow R, Engels EA. Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study. Lancet HIV **2017**; 4:e495–504.

6. Massad LS, Hessol NA, Darragh TM, et al. Cervical cancer incidence after up to 20 years of observation among women with HIV. Int J Cancer **2017**; 141:1561–5.

7. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003. Ann Intern Med **2008**; 148:728–36.

8. Robbins HA, Pfeiffer RM, Shiels MS, Li J, Hall HI, Engels EA. Excess cancers among HIV-infected people in the United States. J Natl Cancer Inst **2015**; 107:dju503.

9. Shiels MS, Cole SR, Kirk GD, Poole C. A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. J Acquir Immune Defic Syndr **2009**; 52:611–22.

10. Shiels MS, Pfeiffer RM, Gail MH, et al. Cancer burden in the HIV-infected population in the United States. J Natl Cancer Inst **2011**; 103:753–62.

11. Samji H, Cescon A, Hogg RS, et al; North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. PLoS One **2013**; 8:e81355.

12. Centers for Disease Control and Prevention. Diagnoses of HIV infection among adults aged 50 years and older in the United States and dependent areas, 2010–2014. HIV Surveillance Suppl Rep **2016**; 21:1–69.

13. Centers for Disease Control and Prevention. Diagnoses of HIV infection in the United States and dependent areas, 2014. HIV Surveillance Rep **2014**; 26:1–123.

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

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

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

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

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

19. He L, Pan X, Dou Z, et al. The factors related to CD4$^+$ T-cell recovery and viral suppression in patients who have low CD4$^+$ T cell counts at the initiation of HAART: a retrospective study of the national HIV treatment sub-database of Zhejiang Province, China, 2014. PLoS One **2016**; 11:e0148915.

20. Fritz A, Percy C, Jack A, et al. International classification of diseases for oncology. 3rd ed. 1st revision. Geneva, Switzerland: World Health Organization, **2013**.

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

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

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

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

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

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

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

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

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

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

31. Pantanowitz L, Dezube BJ. Reasons for a deficit of breast cancer among HIV-infected patients. J Clin Oncol **2004**; 22:1347–50.

32. Frisch M, Biggar RJ, Engels EA, Goedert JJ; AIDS-Cancer Match Registry Study Group. Association of cancer with AIDS-related immunosuppression in adults. JAMA **2001**; 285:1736–45.

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

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

35. Coghill AE, Engels EA, Schymura M, Mahale P, Shiels MS. Lower risks of breast, prostate, and colorectal cancers among HIV-infected individuals in the United States. J Natl Cancer Inst **2017**; In press.

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

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

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

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

40. Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas, 2014. HIV Surveillance Suppl Rep 21(4). Available at: http://www.cdc.gov/hiv/library/reports/surveillance. Accessed 22 December 2017.