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Cumulative Incidence of Cancer Among Persons With HIV in North America

A Cohort Study

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Background: Cancer is increasingly common among persons with HIV.

Objective: To examine calendar trends in cumulative cancer incidence and hazard rate by HIV status.

Design: Cohort study.

Setting: North American AIDS Cohort Collaboration on Research and Design during 1996 to 2009.

Participants: 86 620 persons with HIV and 196 987 uninfected adults.

Measurements: Cancer type–specific cumulative incidence by age 75 years and calendar trends in cumulative incidence and hazard rates, each by HIV status.

Results: Cumulative incidences of cancer by age 75 years for persons with and without HIV, respectively, were as follows: Kaposi sarcoma, 4.4% and 0.01%; non-Hodgkin lymphoma, 4.5% and 0.7%; lung cancer, 3.4% and 2.8%; anal cancer, 1.5% and 0.05%; colorectal cancer, 1.0% and 1.5%; liver cancer, 1.1% and 0.4%; Hodgkin lymphoma, 0.9% and 0.09%; melanoma, 0.5% and 0.6%; and oral cavity/pharyngeal cancer, 0.8% and 0.8%. Among persons with HIV, calendar trends in cumulative incidence and hazard rate decreased for Kaposi sarcoma and non-Hodgkin lymphoma. For anal, colorectal, and liver cancer, increasing cumulative incidence, but not hazard rate trends, were due to the decreasing mortality rate trend (−9% per year), allowing greater opportunity to be diagnosed. Despite decreasing hazard rate trends for lung cancer, Hodgkin lymphoma, and melanoma, cumulative incidence trends were not seen because of the compensating effect of the declining mortality rate.

Limitation: Secular trends in screening, smoking, and viral co-infections were not evaluated.

Conclusion: Cumulative cancer incidence by age 75 years, approximating lifetime risk in persons with HIV, may have clinical utility in this population. The high cumulative incidences by age 75 years for Kaposi sarcoma, non-Hodgkin lymphoma, and lung cancer support early and sustained antiretroviral therapy and smoking cessation.

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* Drs. Silverberg and Lau contributed equally to this work.

† For members of the North American AIDS Cohort Collaboration on Research and Design of the International Epidemiologic Databases to Evaluate AIDS, see **Appendix 1** (available at www.annals.org).

Antiretroviral therapy (ART) has prolonged the lifespan of persons with HIV (1, 2), resulting in an increasing number of persons aging with HIV (3). Cancer is increasingly common in this population (4), with a higher burden than the general population due to both impaired immune function, including chronic inflammation (4–12), and a higher prevalence of risk factors, including smoking (13–16) and viral co-infections (17–19). Among persons with HIV, the incidence of AIDS-defining cancer, primarily Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL), has declined substantially in the ART era but remains higher than that among uninfected persons (20, 21). Furthermore, the incidence of several types of non–AIDS-defining cancer (NADC), including Hodgkin lymphoma (HL) and lung, anal, and oral cavity/pharyngeal (OP) cancer, is also elevated in persons with HIV (10, 22–26).

Calendar trends in cancer incidence among persons with HIV have been evaluated using several metrics, including numbers of cases (4), incidence rates (4, 27, 28), and cumulative incidence (20). Although the number of cases of virtually all types of NADC has increased due to the growth and aging of the population with HIV (4), there have been inconsistent trends in cancer type–specific incidence rates (**Appendix Table 1**, available at www.annals.org). One reason for the inconsistent results may be that only 1 previous study (20) explicitly accounted for the competing risk for death, which is germane given both the higher mortality risk for persons with HIV than the general population and the dramatic improvements in survival over time for persons with HIV receiving ART.

Our primary objective was to compare time trends in cumulative cancer incidence in persons with and without HIV. We used competing risk methods to evaluate trends in both cumulative incidence (29) and cancer-specific hazard rates (30) to provide a more thorough understanding of the reasons for observed

EDITORS' NOTES

Context

Cancer has become more common among persons with HIV. It is uncertain whether this is simply due to persons living longer.

Contribution

After examination of cumulative cancer incidence by age 75 years and calendar trends in cumulative incidence and hazard rates, it was determined that the cumulative incidences of anal, colorectal, and liver cancers are increasing among persons with HIV primarily because they are living longer. The highest cumulative incidences were seen for Kaposi sarcoma, non-Hodgkin lymphoma, and lung cancer.

Implication

These findings may permit more targeted cancer screening and prevention efforts in persons with HIV.

changes in cancer risk over time, which could be influenced by both the incidence rate of the cancer of interest and the all-cause mortality rate (31, 32). In addition, we report cumulative cancer incidence (that is, cancer risk) by age 75 years, a measure that may have clinical and public health utility in this population because 75 years approximates the current lifespan for effectively treated adults with HIV (1). This metric may be a more intuitive measure of cancer burden than the incidence rate and thus may have greater clinical utility.

METHODS

Study Design, Setting, and Participants

Our objective was to estimate the cumulative incidence of 9 common cancer types by HIV status and calendar period. The study population consisted of adults (≥18 years) followed between 1996 and 2009 in 16 cohorts from the United States and Canada participating in the NA-ACCORD (North American Cohort Collaboration on Research and Design) (**Appendix Table 2**, available at www.annals.org) (33). All contributing cohorts submitted comprehensive clinical data on persons with HIV using standardized data collection methods. In addition, 5 cohorts contributed data on uninfected persons (**Appendix Table 2**) selected to be demographically similar to the persons with HIV in the respective cohorts. Institutional review board approval was obtained for each participating cohort.

Cancer Diagnosis Validation

The end points were the following 9 common incident cancer types: KS; NHL; lung, anal, colorectal, liver, and OP cancers; HL; and melanoma. Persons were evaluated for the first occurrence of a specific type of cancer but could contribute follow-up and events for each cancer type. We collected diagnoses using a Web-based standardized abstraction protocol that included collection of cancer site and histopathology data by manually reviewing medical records and pathology reports or by cancer registry linkage (**Appendix 2**, available at www.annals.org).

Statistical Analysis

For each participant, observation began 3 months after the latest of 1 January 1996, NA-ACCORD entry date, or cohort-specific start date for reporting validated cancer diagnoses (**Appendix Table 2**). The 3-month window allowed for exclusion of prevalent cancer. Each participant was followed until the earliest of 31 December 2009, cancer diagnosis date, death date, date lost to follow-up, or cohort-specific end date for reporting validated cancer diagnoses (**Appendix Table 2**).

In all analyses, we used age as the time scale, which accounted for the potentially strong confounding effect of age on time trends (34). We focused on cumulative cancer incidence by age 75 years as our main measure because this age approximates both the current lifespan for effectively treated adults with HIV and the upper age limit of our follow-up, with 2% and 3% of person-time after age 70 years for persons with and without HIV, respectively. Given the limited follow-up in older ages, we also present cancer risk by age 65 years. Because we did not actually follow persons from age 18 to 75 years but at most followed a given person for 14 years, the cumulative incidence metric relied on the assumption that the age-specific risk for cancer remained constant across birth cohorts, similar to assumptions made for life expectancy calculations (35).

We used a competing risk approach with nonparametric estimators for the competing risk for death (30, 36, 37) to estimate cumulative cancer incidence by HIV status and calendar era, categorized as 1996 to 1999 (reference), 2000 to 2004, and 2005 to 2009. We estimated 95% CIs for cumulative incidence by bootstrap methods (38). Next, we computed the subdistribution hazard ratio (sdHR) (29) to estimate secular changes in cumulative cancer incidence and the cause-specific hazard ratio (csHR) (30) to estimate secular changes in the cancer-specific hazard rate, both adjusted for sex, race (white; black; and other, including Hispanic or unknown), and study cohort. We assessed linear annual trends by assigning a score corresponding with each calendar era midpoint. Proportionality of hazards assumption was assessed by interaction terms between calendar era and age for sdHRs and Schoenfeld residuals (39) for csHRs. Evaluating cumulative incidence using a competing risk approach, along with sdHRs and csHRs, can provide valuable insights into the reasons for changes in cancer risk over time, which may be due to both shifting cancer cause and improvements in overall survival (40). In particular, in the HIV setting with improved survival due to more effective ART, more persons remain alive to potentially have cancer. Thus, even if the hazard rate (csHR) for a cancer type did not change over time, the cumulative incidence (sdHR) would be expected to increase due to the declining death rate.

Table 1. Calendar Trends for Selected Characteristics, by HIV Infection Status, NA-ACCORD, 1996–2009*

Characteristic	1996–1999	2000–2004	2005–2009
Persons with HIV (n = 86 620)			
Person-years	79 351	204 240	192 069
Median age (IQR), *y*†	42 (36–49)	44 (37–51)	47 (40–54)
Median year of birth (IQR)†	1955 (1949–1961)	1957 (1950–1964)	1959 (1952–1966)
Men, %†	87	85	86
Receiving ART, %†	39	67	74
Median CD4$^+$ cell count (IQR), × 10^9 *cells/L*†	0.309 (0.152–0.490)	0.350 (0.187–0.545)	0.382 (0.222–0.570)
Median HIV RNA level (IQR), *copies/mL*†	2729 (400–27 744)	748 (100–21 321)	244 (100–11 018)
Race, %†			
White	45	44	43
Black	43	40	39
Hispanic	3	7	7
Other	2	3	3
Unknown	6	7	8
HIV risk group, %†‡			
MSM	39	42	43
IDU	24	19	17
Other	22	25	25
Unknown	15	14	15
HBV–infected, %†§	3	4	4
HCV–infected, %†§	22	21	20
Crude mortality rate (95% CI) per 100 000 person-years	5140 (4985–5301)	3913 (3828–3999)	2844 (2770–2921)
Uninfected persons (n = 196 987)			
Person-years	306 569	669 647	871 716
Median age (IQR), *y*†	42 (36–49)	45 (38–52)	48 (41–55)
Median year of birth (IQR)†	1955 (1948–1961)	1956 (1949–1963)	1957 (1950–1964)
Men, %†	93	93	93
Race, %†			
White	40	38	38
Black	24	23	24
Hispanic	5	5	5
Other	7	7	7
Unknown	23	26	25
Crude mortality rate (95% CI) per 100 000 person-years	669 (641–699)	870 (848–892)	863 (844–883)

ART = antiretroviral therapy; HBV = hepatitis B virus; HCV = hepatitis C virus; IDU = injection drug user; IQR = interquartile range; MSM = men who have sex with men; NA-ACCORD = North American AIDS Cohort Collaboration on Research and Design.
* Percentages may not sum to 100 due to rounding.
† At entry into calendar era.
‡ 1 large cohort that did not have information on the HIV risk group was omitted.
§ 3 cohorts that did not provide information on HBV infection and 2 cohorts that did not provide information on HCV infection were omitted. Also, these are minimum values because, in the cohorts that did provide information, most participants were not tested.

We used SAS, version 9.3 (SAS Institute), to calculate the nonparametric cumulative incidence functions with an in-house programmed macro based on the PROC PHREG procedure in SAS. We used Stata, version 13 (StataCorp), to estimate the subdistribution and cause-specific proportional hazards models with the stcrreg and stcox commands, respectively. Figures were created in R, version 3.1.0 (R Foundation for Statistical Computing).

Role of the Funding Source

This study was funded by the National Institutes of Health. The funding source had no role in the design, conduct, or analysis of the study or in the decision to submit the manuscript for publication.

RESULTS

This investigation included 86 620 persons with HIV (475 660 person-years) and 196 987 uninfected persons (1 847 932 person-years) (Appendix Table 2). Most participants were men, and fewer than one half were known to be white (Table 1). The median age at entry into the calendar eras of 1996 to 1999 and 2005 to 2009 increased from 42 to 47 years for persons with HIV and from 42 to 48 years for uninfected persons. The median birth year at calendar era entry increased from 1955 to 1959 for persons with HIV and from 1955 to 1957 in uninfected persons, with substantial birth cohort overlap across calendar eras. Among persons with HIV, the median CD4$^+$ count increased from 0.309 to 0.382 × 10^9 cells/L, and despite increasing age, the crude mortality rate decreased from 5140 to 2844 deaths per 100 000 person-years. However, even in 2005 to 2009, the mortality rate in persons with HIV was more than 3 times higher than that in uninfected persons. During 1996 to 2009, each cancer type–specific incidence rate was higher among persons with HIV than uninfected persons (Table 2), most notably for KS, NHL, anal cancer, and HL.

Cumulative Cancer Incidence

Cumulative cancer incidence by ages 65 and 75 years during 1996 to 2009 was higher among persons with HIV than uninfected persons for all cancer types

Table 2. Crude Cancer Type–Specific Incidence Rates and All-Cause Death Rates, by HIV Infection Status, NA-ACCORD, 1996–2009

Event	Persons With HIV		Uninfected Persons	
	Persons, *n*	Incidence Rate per 100 000 Person-Years	Persons, *n*	Incidence Rate per 100 000 Person-Years
Kaposi sarcoma	612	130.4	3	0.2
Non-Hodgkin lymphoma	725	153.5	233	12.6
Lung cancer	614	129.3	839	45.4
Anal cancer	285	60.1	22	1.2
Colorectal cancer	173	36.4	510	27.7
Liver cancer	220	46.3	201	10.9
Hodgkin lymphoma	159	33.5	36	1.9
Melanoma	78	16.4	268	14.5
Oral cavity/pharyngeal cancer	163	34.3	340	18.4
Death	17 534	3686.0	15 400	833.0

NA-ACCORD = North American AIDS Cohort Collaboration on Research and Design.

except colorectal cancer, melanoma, and OP cancer (Table 3). Among persons with HIV during 1996 to 2009, cumulative incidence by age 75 years was highest for KS (4.4%), NHL (4.5%), and lung cancer (3.4%); in the most recent calendar era (2005 to 2009), it was 4.1% for KS, 4.0% for NHL, and 3.7% for lung cancer (Figure 1). Among uninfected persons during 1996 to 2009, cumulative incidence by age 75 years was greater than 2% only for lung cancer (2.8%); in 2005 to 2009, it was highest for lung (2.3%) and colorectal (1.3%) cancer (Figure 2).

Calendar Trends in Cumulative Incidence

Among persons with HIV, we saw significant declining annual trends in cumulative incidence, as measured by the sdHR (Table 4), for KS (−4% per year), NHL (−5% per year), and death (−9% per year) and significant increasing trends for anal (6% per year), colorectal (5% per year), and liver (6% per year) cancer. We saw no evidence for cumulative incidence trends for lung cancer, HL, melanoma, or OP cancer; however, given the wide CIs for HL, melanoma, and OP cancer, the absence of trends cannot be confirmed. Among uninfected persons, we saw significant declining trends in cumulative incidence for lung cancer (−5% per year), colorectal cancer (−6% per year), melanoma (−7% per year), OP cancer (−6% per year), and death (−3% per year) but no significant increasing trends. Cumulative incidence trends significantly differed by HIV status for NHL, which decreased only in persons with HIV; colorectal cancer, which increased in persons with HIV but decreased in uninfected persons; lung and OP cancer, both of which decreased only in uninfected persons; and death, for which there was a greater decline in persons with HIV.

Calendar Trends in Hazard Rates

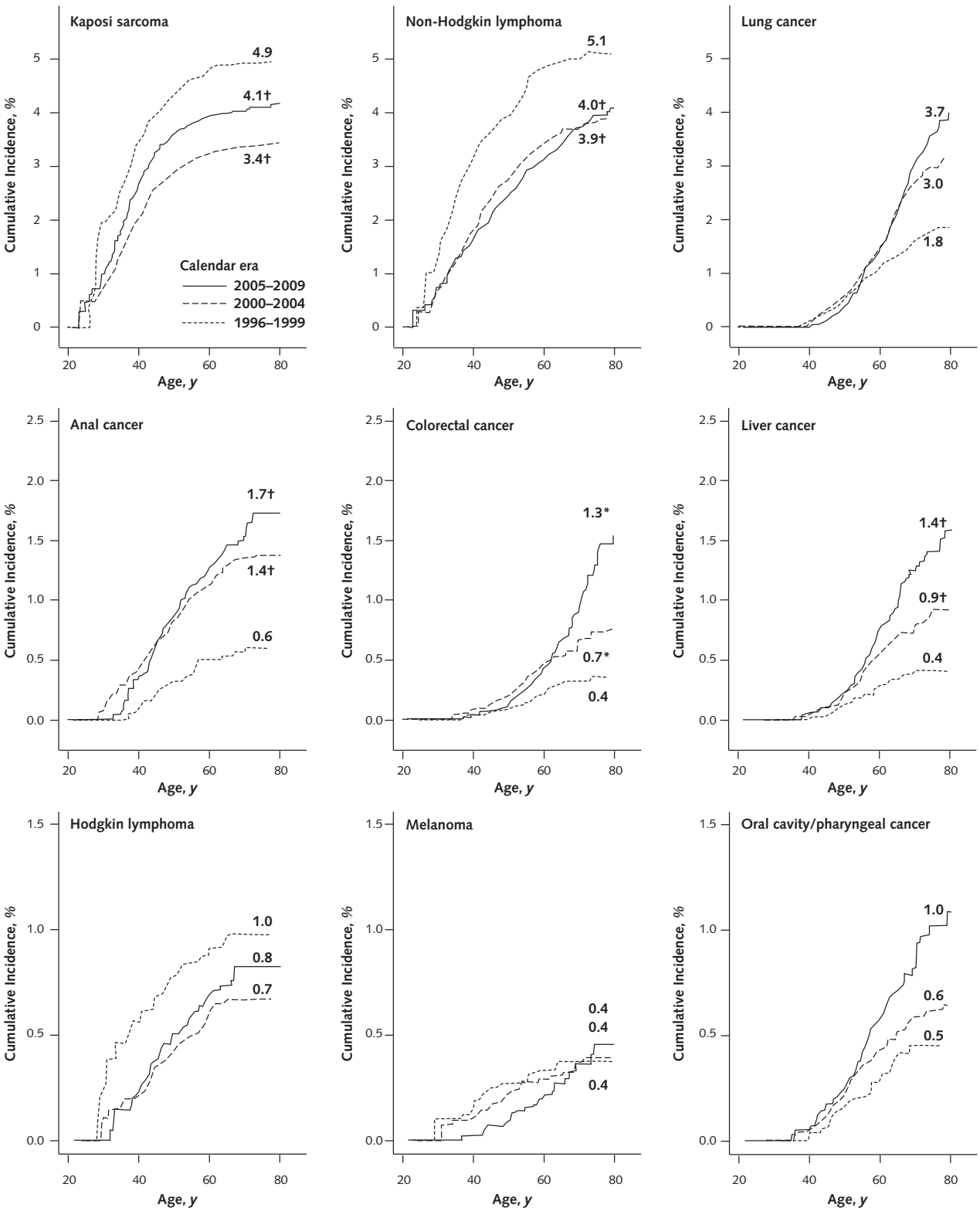
Among persons with HIV, we saw significant declining annual trends in hazard rate, as measured by the csHR (Table 4), for KS (−6% per year), NHL (−8% per year), lung cancer (−4% per year), HL (−5% per year), melanoma (−6% per year), and death (−9% per year). For anal cancer, although the annual calendar trend was not significant, there was evidence of a nonlinear trend, with similarly increased hazard rates in 2000 to 2004 and 2005 to 2009 compared with 1996 to 1999 (Appendix Table 3, available at www.annals.org). We saw no evidence for hazard rate trends for colorectal, liver, or OP cancer, although the absence of trends cannot be confirmed given the wide CIs. Among uninfected persons, we saw significant declining trends in the hazard rate for lung cancer (−6% per year), colo-

Table 3. Crude Cumulative Cancer Incidence by Ages 65 y and 75 y for Patients With and Without HIV, NA-ACCORD, 1996–2009

Cancer Type	Incidence (95% CI), %			
	Persons With HIV		Uninfected Persons	
	65 y	75 y	65 y	75 y
Kaposi sarcoma	4.3 (3.8–5.0)	4.4 (3.8–5.2)	0 (0–0.01)	0.01 (0–0.03)
Non-Hodgkin lymphoma	4.1 (3.6–4.6)	4.5 (4.0–5.1)	0.4 (0.3–0.4)	0.7 (0.6–0.8)
Lung	2.2 (2.0–2.4)	3.4 (3.1–3.7)	1.3 (1.1–1.4)	2.8 (2.5–3.0)
Anal	1.3 (1.1–1.5)	1.5 (1.3–1.7)	0.03 (0.02–0.04)	0.05 (0.03–0.08)
Colorectal	0.6 (0.5–0.7)	1.0 (0.8–1.2)	0.8 (0.7–0.9)	1.5 (1.3–1.6)
Liver	0.8 (0.7–0.9)	1.1 (1.0–1.3)	0.3 (0.3–0.4)	0.4 (0.3–0.5)
Hodgkin lymphoma	0.9 (0.7–1.0)	0.9 (0.7–1.1)	0.06 (0.04–0.08)	0.09 (0.05–0.12)
Melanoma	0.4 (0.3–0.5)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	0.6 (0.5–0.7)
Oral cavity/pharyngeal	0.6 (0.5–0.7)	0.8 (0.7–1.0)	0.6 (0.5–0.6)	0.8 (0.7–1.0)

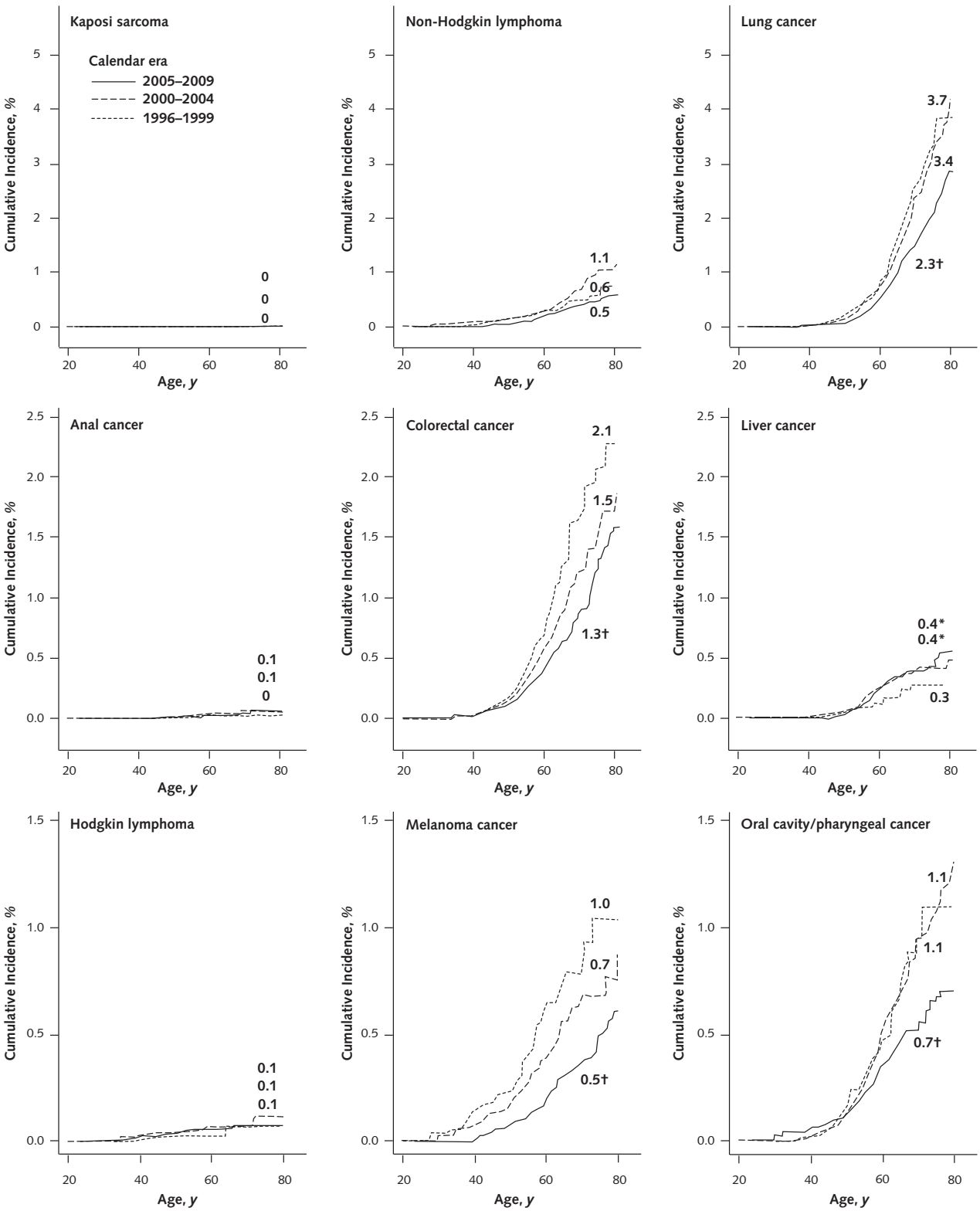
NA-ACCORD = North American AIDS Cohort Collaboration on Research and Design.

Figure 1. Cumulative cancer incidence for persons with HIV, by calendar era and cancer type with age as the time scale, NA-ACCORD, 1996–2009.



Cumulative incidence (i.e., cancer risk) curves were obtained using nonparametric estimators for competing risk events. Numbers associated with curves represent cumulative incidence by age 75 y. NA-ACCORD = North American AIDS Cohort Collaboration on Research and Design.
* $P < 0.05$ compared with reference (1996–1999 era).
† $P < 0.01$ compared with reference (1996–1999 era).

Figure 2. Cumulative cancer incidence for uninfected persons, by calendar era and cancer type with age as the time scale, NA-ACCORD, 1996–2009.



Cumulative incidence (i.e., cancer risk) curves were obtained using nonparametric estimators for competing risk events. Numbers associated with curves represent cumulative incidence by age 75 y. NA-ACCORD = North American AIDS Cohort Collaboration on Research and Design.
* $P < 0.05$ compared with reference (1996–1999 era).
† $P < 0.01$ compared with reference (1996–1999 era).

Table 4. Calendar Trends in Cancer and Mortality Cumulative Incidence and Hazard Rates by HIV Infection Status, NA-ACCORD, 1996–2009

Event	Cumulative Incidence Annual Trend			Cause-Specific Hazard Rate Annual Trend		
	sdHR (95% CI), %*	*P* Value	Interaction *P* Value†	csHR (95% CI), %‡	*P* Value	Interaction *P* Value†
Kaposi sarcoma						
HIV-infected	−4 (−7 to −2)	<0.001	–	−6 (−8 to −4)§	<0.001	–
Uninfected	Too few events to estimate trends		–	Too few events to estimate trends		–
Non-Hodgkin lymphoma						
HIV-infected	−5 (−7 to −3)§	<0.001	–	−8 (−10 to −6)	<0.001	–
Uninfected	0 (−4 to 3)§	0.85	0.015	−2 (−5 to 2)	0.40	0.002
Lung cancer						
HIV-infected	−1 (−3 to 2)§	0.59	–	−4 (−7 to −3)	<0.001	–
Uninfected	−5 (−6 to −3)§	<0.001	0.008	−6 (−8 to −4)	<0.001	0.42
Anal cancer						
HIV-infected	6 (2 to 9)	0.002	–	3 (−1 to 7)	0.130	–
Uninfected	4 (−7 to 17)	0.47	0.84	3 (−9 to 17)	0.61	0.95
Colorectal cancer						
HIV-infected	5 (1 to 10)	0.020	–	2 (−3 to 7)	0.44	–
Uninfected	−6 (−8 to −3)	<0.001	<0.001	−7 (−9 to −4)	<0.001	0.001
Liver cancer						
HIV-infected	6 (2 to 11)	0.002	–	2 (−2 to 7)	0.28	–
Uninfected	4 (−1 to 8)	0.100	0.39	2 (−2 to 7)	0.28	0.96
Hodgkin lymphoma						
HIV-infected	−2 (−6 to 3)	0.41	–	−5 (−9 to 0)	0.050	–
Uninfected	3 (−6 to 12)	0.56	0.37	2 (−8 to 12)	0.75	0.25
Melanoma						
HIV-infected	−4 (−10 to 3)	0.24	–	−6 (−12 to 0)	0.050	–
Uninfected	−7 (−10 to −4)	<0.001	0.38	−8 (−11 to −5)	<0.001	0.71
Oral cavity/pharyngeal cancer						
HIV-infected	3 (−2 to 7)	0.25	–	−1 (−5 to 4)	0.82	–
Uninfected	−6 (−9 to −3)	<0.001	0.001	−7 (−10 to −4)	<0.001	0.010
Death¶						
HIV-infected	−9 (−9 to −8)§	<0.001	–	−9 (−9 to −8)§	<0.001	–
Uninfected	−3 (−3 to −2)§	<0.001	<0.001	−3 (−3 to −2)§	<0.001	<0.001

csHR = cause-specific hazard ratio; NA-ACCORD = North American AIDS Cohort Collaboration on Research and Design; sdHR = subdistribution hazard ratio.
* Measures annual calendar changes in cumulative incidence, adjusted for sex, race, and cohort.
† HIV-infected vs. uninfected for corresponding trend.
‡ Measures annual calendar changes in hazard rates, adjusted for sex, race, and cohort.
§ Evidence of violation of proportional hazards assumption. Estimate should be interpreted as a weighted average over all ages.
¶ Analysis in which melanoma was the competing event.

rectal cancer (−7% per year), melanoma (−8% per year), OP cancer (−7% per year), and death (−3% per year). Cancer-specific hazard rate trends significantly differed by HIV status for NHL, which declined only in persons with HIV; colorectal and OP cancer, which declined only in uninfected persons; and death, which declined more in persons with HIV than in uninfected persons. Furthermore, persons with and without HIV had similar declining trends for lung cancer and melanoma.

DISCUSSION

In this investigation, we reported cumulative cancer incidence by age 75 years, a novel use of this measure in the population with HIV that provides easily interpretable information for persons with HIV about their long-term cancer risk. Our results indicated that KS, NHL, and lung cancer remain of great concern, each with lifetime risks of approximately 1 in 25 in 2005 to 2009. In addition, the competing risk approach helped disentangle the effects of improved survival and changing cancer-specific hazard rates on cumulative incidence trends.

Of 7 NADCs examined here, we saw increasing cumulative incidence over time for anal, colorectal, and liver cancer among persons with HIV. It seems that 2 factors contributed to this trend for anal cancer: the

declining death rate, which presumably allowed more persons to survive long enough to have long-term exposure to human papillomavirus (HPV) infection (41), and the elevated hazard rate of anal cancer after 1996 to 1999. The observed stabilization of the hazard rate at an elevated level after 1999, consistent with our previous, more detailed investigation of anal cancer in NA-ACCORD (42), may be due to improved immune function associated with more recently available ART compared with the early ART era (that is, 1996 to 1999) because previous studies have suggested an inverse relationship between $CD4^+$ count and anal cancer incidence rates (10). However, calendar trends in incidence rates (similar to the trends in hazard rates here) reported by others for anal cancer have not been consistent (**Appendix Table 1**) (27, 43–46).

The increasing cumulative incidence trends for liver and colorectal cancer among persons with HIV seemed to be due primarily to the declining death rate, because an increasing trend was not seen in the csHRs for these 2 cancer types. For liver cancer, the increasing cumulative incidence trend for persons with HIV was similar in magnitude and not statistically different from the trend for liver cancer among uninfected persons. This similarity may reflect the identical nonsignificant increasing hazard rate trends between persons with and without HIV, consistent with a general increase in liver cancer risk for "baby boomers" (that is, birth years from 1945 to 1965), who have a higher prevalence of hepatitis C virus (HCV) and hepatitis B virus (HBV) infection than other birth cohorts (47). For colorectal cancer, the increasing cumulative incidence trend among persons with HIV was in the opposite direction of the significant decreasing cumulative incidence and hazard rate trends among our uninfected persons—a decrease that was also seen in the general population (48). We hypothesize that this disparity in colorectal cancer trends may be because persons with HIV lag behind the trend of increased colorectal cancer screening in the general population (49).

Among persons with HIV, we found no evidence for calendar trends in cumulative incidence for 4 other types of NADC (lung cancer, HL, melanoma, or OP cancer). For lung cancer, HL, and melanoma, we did not see cumulative incidence trends despite decreasing hazard rate trends, implying that the declining mortality rate counterbalanced the declining cancer-specific hazard rates. Of note, for lung cancer, we saw similar declining trends in hazard rates for persons with and without HIV, which is consistent with trends in the general population (48) due to a long-term decline in smoking prevalence (50). This finding is consistent with similarly declining smoking prevalence by HIV status, suggesting that the disparity in cumulative incidence trends, which are steady in persons with HIV and are declining in uninfected persons, was due to the much greater decreasing trends of mortality rates in persons with HIV.

For melanoma, the significant declining trends in hazard rates among both persons with and without HIV were the opposite of those seen in the general population, although only among white persons (48), whereas less than one half of our sample was known to be white. We speculate but cannot confirm that there was more skin cancer screening or reduced sun exposure over time among our study participants compared with the general population.

For OP cancer, both the cumulative incidence and hazard rate trends significantly declined among uninfected persons; no trends were observed among persons with HIV. In the general population, incidence rates of OP cancer declined from 1992 to 2010, except during 2003 to 2010 in men (48). In general, overall incidence trends in OP cancer are determined by trends in OP cancer related to HPV, which has been increasing in the general population, and in OP cancer unrelated to HPV, which is strongly associated with smoking and alcohol consumption and has been decreasing in the general population (51–53).

As expected, the cumulative incidences for KS and NHL declined significantly for persons with HIV, with even stronger decreases in hazard rates, consistent with previous studies (4, 22, 23, 28, 54, 55) and resulting from viral suppression and consequent improved immune function afforded by ART. In contrast, the cumulative incidence and hazard rate trends for NHL did not change over time among uninfected persons, confirming that successful ART has reduced the gap in NHL risk by HIV status (23, 27, 56). We could not compare trends similarly for KS by HIV status because only 3 uninfected persons had KS.

The only other studies to use competing risk methods to estimate cumulative cancer incidence in immunosuppressed populations were done in persons with AIDS (20) and organ transplant recipients (57) and thus are not directly comparable to our study. Few recent studies have evaluated trends in incidence rates for specific types of NADC among persons with HIV exclusively in the ART era, similar to our evaluation of calendar csHR trends (27, 42–46). Across studies, trends for incidence rates, analogous to those for hazard rates, have been indeterminate (that is, not statistically significant) or decreasing for lung cancer, HL, and melanoma; indeterminate or increasing for anal (except for 1 study with a decreasing trend) and liver cancer; and indeterminate for colorectal and OP cancer (**Appendix Table 1**). Differences across studies may be due to differences in statistical power, time periods analyzed, or prevalence of risk factors or cancer screening.

Our results have clinical implications about cancer screening in persons with HIV. Annual lung cancer screening with low-dose computed tomography is recommended for heavy smokers aged 55 to 80 years in the general population (58). The high smoking prevalence in persons with HIV, along with lung cancer incidence similar to that of AIDS-defining cancer, suggests that smokers with HIV should be compelling candidates for screening. However, research is urgently needed to inform lung cancer screening policy for persons with HIV by clarifying the benefits versus harms of screening, because there is potential for harms resulting from a high false-positive rate due to elevated incidence of lung infections and other pulmonary diseases (59). The

increase in colorectal cancer risk among persons with HIV, despite a decline in the general population, indicated the need for increased screening among persons with HIV aged 50 to 75 years, as recommended for the general population (60). Furthermore, the increase in anal cancer risk highlights the need for further evidence about the harms and benefits of anal dysplasia screening (61). Although there are no formal guidelines, it would be prudent for physicians to be alert for early signs and symptoms of KS and NHL.

Our results also have clinical implications for primary prevention. Development of targeted smoking cessation interventions for persons with HIV is an obvious priority. The highly effective HPV vaccine was licensed in 2011 for prevention of anal cancer (62). Although there is concern that high prevalence of HPV infection among persons with HIV may render vaccination ineffective, the vaccine has, in fact, been found to be immunogenic in persons with HIV (63–65). This suggests that vaccination has the potential to substantially decrease the burden of anal and possibly HPV-related OP cancer, although further research is clearly needed. The increasing risk for liver cancer over time indicates a need to ensure universal HBV vaccination for persons with HIV who are HBV-seronegative, as already recommended (66), and to provide treatment of HBV infection using ART regimens with anti-HBV activity (66) and of HCV infection with recently approved interferon-free therapies (67, 68). Despite the calendar trend declines in AIDS-defining cancer among persons with HIV, KS and NHL remain major concerns such that efforts need to be intensified to promote early, sustained ART, the only known approach to prevention of these and possibly other cancer types linked to immunosuppression (10) or inflammation (12). Research is needed to follow up on observational studies that suggest that statin use by persons with HIV may reduce cancer risk (69–71), presumably because of the anti-inflammatory effects (72).

Our study has limitations. First, we did not include secular trends in cancer screening, smoking, or viral co-infections in our models because we did not comprehensively capture this information across cohorts, especially among uninfected persons and noncancer cases. However, among persons with HIV with available data, we found the prevalence of HBV and HCV infection to be constant over calendar eras. We also chose not to adjust for $CD4^+$ and HIV RNA because these factors are so intertwined with the survival improvements for persons with HIV. Second, although our cancer validation ensured a standardized approach for cancer case ascertainment across cohorts, it is possible that differences in screening resulted in variable ascertainment. However, variation in screening is not limited to our study population and would almost certainly be found also in the general U.S. and Canadian populations with HIV. Third, our measure of cumulative incidence relied on age-specific follow-up for only a small portion of each participant's adult lifetime, under the assumption that the age-specific risk for cancer remained constant by birth cohort. We believe that this assumption is reasonable because our study sample included a relatively narrow birth cohort range, with substantial birth cohort overlap across calendar eras, similar variability within each calendar era, and similar birth cohort representation among persons with and without HIV. Nevertheless, some of our findings may have been driven in part by birth cohort effects, which would tend to manifest as artificially steep cumulative incidence increases with age if earlier birth cohorts had a higher risk for cancer, such as the risk by birth cohorts shown for lung cancer in the general population (73). Fourth, there was limited follow-up in older ages, although comparison of cumulative cancer incidence estimates by ages 65 and 75 years demonstrated that higher cancer risk at older ages noticeably influenced results for some cancer types. Fifth, nonsignificant trends associated with relatively wide CIs do not necessarily indicate the true absence of trends. Finally, although the persons with HIV in NA-ACCORD are highly generalizable to populations with HIV in the United States and Canada (33), the proportion of women and Hispanics was low, and the uninfected persons may be less generalizable. However, with respect to the uninfected group, exchangeability with the group with HIV is more important for study inferences than generalizability (74).

A major strength of our study was that we accounted for the competing risk for death, which allowed for a detailed assessment of whether trends in cumulative incidence resulted from actual changes in the cancer type–specific hazard rate versus reductions in the all-cause mortality rate (31, 32). This approach also provided estimates of the cumulative incidence of cancer by age 75 years, a measure that has not been reported previously in this population and may have clinical and public health utility. This study was also one of few with a demographically similar uninfected group (43, 75), which may reduce biases relating to access to care, surveillance for cancer, or prevalence of cancer risk factors that can occur when general population comparison groups are used.

In summary, the effectiveness of ART has enabled persons with HIV to live long enough to have cancer. Thus, the increasing cumulative incidence trends for anal, colorectal, and liver cancer and the lack of evidence for trends for lung cancer, HL, and melanoma were driven by the steeply declining mortality rate, without which these trends would have been absent or declining, according to the trends in cancer-specific hazard rates. The high cumulative incidences by age 75 years for KS, NHL, and lung cancer indicate that public health efforts need to be intensified to promote early, sustained ART; smoking cessation; and lung cancer screening. As the population with HIV ages, future estimates of cumulative incidence could be stratified by levels of cancer risk factors, such as $CD4^+$ cell count, smoking, alcohol consumption, and HBV or HCV infection, to more accurately inform patients and providers about risk and to help further target prevention efforts.

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Appendix 1: Members of the NA-ACCORD of the International Epidemiologic Databases to Evaluate AIDS

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Appendix 2: NA-ACCORD Cancer Validation

We developed a standardized process for case finding, validation, categorization, and data collection for all types of incident invasive cancer among persons followed in NA-ACCORD interval and clinical cohorts. We did not collect information on tumors described as benign, in situ, dysplasia, precancer, or premalignant, nor did we collect information on recurrent or second cancer diagnoses of a given type, with the exception of hematologic cancer. In addition to collecting incident cancer diagnoses, we gathered information for prevalent cancer—those preceding entry of a patient into a given cohort—when available. Cohorts were not required to gather additional data outside the cancer registry or medical record systems for these diagnoses. However, any outside documentation contained in the medical record was fully used during the review and data collection process. For remote or historical diagnoses (before a 3-month window preceding entry of a patient into a given cohort), we permitted collection of only the cancer site category and diagnosis date. Every attempt was made to identify and categorize the primary site or location of each cancer diagnosis as per a

predefined NA-ACCORD specific scheme similar to Surveillance, Epidemiology, and End Results site groups. If this was unknown or the only information was that the patient had "cancer," then the diagnosis was labeled as "other."

Step 1: Case Finding and Categorizing Cancer Type

The method for finding cases of cancer differed among cohorts depending on whether linkage with a national or local cancer registry was possible. Cancer diagnoses and characteristics were preloaded into the NA-ACCORD collection database for cancer data from cancer registry coding (International Classification of Diseases for Oncology, Third Edition [ICD-O-3]); cohort-specific diagnostic codes; or health care system diagnostic coding (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9]).

Cancer Registry Cohorts

Nine cohorts used national or local cancer registries to find validated cancer cases. We provided each cohort with individualized and detailed information on how to map and convert ICD-O-3 codes from registry diagnoses to standard NA-ACCORD–specific cancer site and histology categories. Because these cases were from cancer registries, they were considered validated without requiring additional clinical chart review. However, medical records were often reviewed to verify diagnoses and collect additional information as described below.

Non–Cancer Registry Cohorts

Eight cohorts had no registry access and searched electronic medical record systems for cohort-specific or ICD-9 diagnostic codes to find preliminary cancer cases (data for one of these cohorts were not available for the current study). Cohorts were provided with detailed information on how to map and convert ICD-9 codes to standard NA-ACCORD–specific cancer site categories. These preliminary cases were then reviewed and verified on an individual basis as per the process described in step 2, below.

Step 2: Case Review, Data Collection, and Validation

Once cases were identified and loaded into the database, local review of electronic or paper medical records was done by trained medical record abstracters under the supervision of a physician to validate the diagnosis; verify NA-ACCORD cancer categories and diagnosis dates; and collect additional standardized information on diagnosis certainty (supporting documentation), histology, and other variables. Certain cohorts with cancer registry–verified cancer did not do additional record review and simply converted registry data into standardized NA-ACCORD data variables. In addition to collecting information on cancer site and diagnosis date, we collected detailed information on histopathology, grade, stage, Papanicolaou (Pap) smear screening, family history of cancer, number of live births (women), and exposure to alcohol and tobacco. To ensure the integrity of the data, the NA-ACCORD cancer data collection application used drop-down menus and checkboxes to limit free text input and automated checks for missing data. Reviewers were provided with detailed instructions and examples based on cancer data collection instructions from the Surveillance, Epidemiology, and End Results program to determine the most accurate cancer diagnosis category and date. For erroneous cancer diagnoses (no supporting information to confirm the diagnosis, cancer recurrence, or second occurrence of a given cancer type), no further data collection was done. Information on histopathology was considered essential for all cancer cases and the most reliable source of information for validating a cancer diagnosis. If histopathology was not found, then other types of information supporting the diagnosis were collected as follows:

a. Endoscopy: Laryngoscopy, esophagogastroduodenoscopy, bronchoscopy, colonoscopy, or colposcopy with findings that supported the cancer diagnosis.

b. Laboratory test: Patient body fluid or tissues sent for laboratory analysis (other than histopathology or cytology) yielded results that supported the cancer diagnosis.

c. Computed tomography or positron emission tomography results that supported the cancer diagnosis.

d. Magnetic resonance imaging results that supported the cancer diagnosis.

e. Ultrasonography results that supported the cancer diagnosis.

f. Other radiography results that supported the cancer diagnosis.

g. Physical examination: A clinician-documented examination with findings that supported the cancer diagnosis (often relevant for KS).

h. Clinician documentation only: A medical record generated from an outpatient or inpatient visit by a clinician within the medical center or site that documented the cancer diagnosis.

i. Outside clinician documentation only: A medical record generated from an outpatient or inpatient visit by a clinician outside the medical center or site that documented the cancer diagnosis.

j. Patient report only: A medical record generated from an outpatient or inpatient visit that documented patient-reported history of the cancer diagnosis (relevant for prevalent historical cancer).

All available records were comprehensively reviewed to obtain histopathology and staging information for every cancer case. If histopathology was not found after thorough review, then histopathology was

considered "unknown." For example, KS was often diagnosed by physical examination with no biopsy performed, in which case histopathology was entered as "unknown." Cancer registry–linked sites obtained histopathology from ICD-O-3 codes and registry staging data collected as TNM stage (such as I, II, IIA, IIB, III, IIIA, IIIB, or IV) or descriptive summary stage (that is, "Localized," "Regional, direct extension only," "Regional, lymph nodes only," Regional, direct extension & lymph nodes," "Regional, NOS," "Distant metastases or systemic disease (Remote)," or "Widespread"). For non-registry cohorts, standardized TNM stage or descriptive summary staging information was collected from clinician documentation, most often from a hematology/oncology clinician encounter at the same institution or an outside facility caring for the patient. Kaposi sarcoma was staged based on a unique classification system into one of the following hierarchical categories: several visceral organs (such as lung, liver, or gastrointestinal tract); lung; liver; gastrointestinal tract (including esophagus but not oropharynx); other visceral organ; oropharynx or other mucosal site; lymph node; skin only, many (≥10) lesions; skin only, few (10) lesions; skin only, number of lesions unknown; and site or extent of disease missing or unknown.

Information on exposure to tobacco and alcohol was collected for persons with all cancer types, classified as never, current, past, or unknown before and up to 6 months after the cancer diagnosis date. If available, information about level of tobacco exposure (current or past) was quantified as packs per day, years, or pack-years of smoking. Level of alcohol exposure (current or past) was quantified as drinks per week or years drinking or qualified as social, daily, abuse, dependence, binge, or unknown. In addition, patient-reported survey data are collected by NA-ACCORD–participating cohorts using standardized audio computer-assisted self-interviewing or interview-administered instruments, including the World Health Organization's Alcohol, Smoking, and Substance Involvement Screening Test and Alcohol Use Disorders Identification Test. These data can be used in combination with information collected through medical record review and clinician-documented diagnosis data to classify an individual's substance abuse by type. Information was also collected on Pap smear screenings done before the date of diagnosis for persons with cervical cancer and number of lifetime live births before cancer diagnosis for all females. Family history of cancer, including degree of relative with the diagnosis when available, was collected for persons with all cancer types. Some cohorts that verified cancer via registry data could not review medical records to collect additional information on Pap smear screening, tobacco, alcohol, family history, or live births.

Appendix Table 1. Comparison Across Studies of Direction of Calendar Trends* in Cancer Incidence Rates Among HIV-Infected Persons in the Antiretroviral Therapy Era

Study, Year (Reference)	Years	Population	Cancer Type						
			Lung	Anal	Colorectal	Liver	Hodgkin Lymphoma	Melanoma	Oral Cavity/ Pharyngeal
Current†	1996-2009	NA-ACCORD	↓	NS‡	NS	NS	↓	↓	NS
Silverberg et al, 2009 (43)	1996-2007	Kaiser Permanente	NS	↓	NS	NS	NS	NS	NS
Silverberg et al, 2012 (42)	1996-2007	NA-ACCORD	–	↑	–	–	–	–	–
Piketty et al, 2012 (44)	1997-2008	French Hospital Database on HIV	–	NS	–	–	–	–	–
Worm et al, 2013 (46)	2004-2010	D:A:D Study	NS	NS	–	–	NS	–	–
Hleyhel et al, 2014 (45)	1997-2009	French Hospital Database on HIV	↓	NS	–	↑	NS	–	–
Robbins et al, 2014 (27)	1996-2010	HIV/AIDS Cancer Match Study	↓	↑	NS	↑	↓	–	–

D:A:D = Data Collection of Adverse Events of Anti-HIV Drugs; NA-ACCORD = North American AIDS Cohort Collaboration on Research and Design; NS = nonsignificant.

* Based on *P* value reported in the prior studies. Trends were denoted as ↑ (i.e., statistically significant increasing trend), ↓ (i.e., statistically significant decreasing trend), or NS (i.e., indeterminate trend with $P > 0.050$).

† Based on cause-specific hazard rate annual calendar trends and *P* values presented in **Table 4**.

‡ Although the cause-specific hazard rate annual trend was NS, there was evidence of a nonlinear increasing trend for anal cancer, as shown in **Appendix Table 3**, similar to reference 42, which was also based on NA-ACCORD data.

Appendix Table 2. Contributing NA-ACCORD Cohorts

Cohort	Participants, *n*	Men, %	Median Age* (IQR), *y*	Calendar Period of Observation
AIDS Link to the IntraVenous Experience (HIV+)	590	70	42 (38–46)	1996–2007
AIDS Link to the IntraVenous Experience (HIV−)	1593	71	42 (37–47)	1996–2007
Case Western Reserve University Immunology Unit Patient Care and Research Database	1582	79	39 (33–45)	1997–2009
HIV Research Network	9245	80	41 (35–47)	2001–2007
Highly Active Antiretroviral Therapy Observational Medical Evaluation and Research	4483	81	40 (34–47)	1996–2008
HIV Outpatient Study	4291	75	39 (34–45)	1996–2009
Johns Hopkins HIV Clinical Cohort	3977	65	39 (34–45)	1996–2008
Kaiser Permanente Northern California (HIV+)	7723	90	40 (34–47)	1996–2008
Kaiser Permanente Northern California (HIV−)	111 558	90	40 (34–47)	1996–2008
Multicenter AIDS Cohort Study (HIV+)	1444	100	41 (37–46)	1996–2008
Multicenter AIDS Cohort Study (HIV−)	2952	100	44 (39–50)	1996–2008
Second Multicenter Hemophilia Cohort Study	170	98	35 (29–42)	2001–2005
Montreal Chest Institute Immunodeficiency Service Cohort	2328	75	39 (33–45)	1997–2009
Southern Alberta Clinic Cohort	1864	81	37 (32–43)	1996–2009
University of North Carolina, Chapel Hill HIV Clinic	1565	70	40 (33–46)	1999–2008
University of Washington HIV Cohort	3004	85	38 (32–44)	1996–2009
Veterans Aging Cohort Study Virtual Cohort (HIV+)	38 926	98	47 (41–53)	1996–2008
Veterans Aging Cohort Study Virtual Cohort (HIV−)	80 114	98	48 (41–54)	1996–2008
Vanderbilt-Meharry Center for AIDS Research Cohort	3083	76	38 (32–45)	1997–2007
Women's Interagency HIV Study (HIV+)	2345	0	36 (31–41)	1996–2008
Women's Interagency HIV Study (HIV−)	770	0	33 (26–39)	1996–2008
Overall HIV+	86 620	86	43 (36–50)	–
Overall HIV−	196 987	93	43 (36–50)	–

IQR = interquartile range; NA-ACCORD = North American AIDS Cohort Collaboration on Research and Design.
* At start of follow-up.

Appendix Table 3. Categorical Calendar Trends in Cancer and Mortality Cumulative Incidence and Hazard Rates, by HIV Infection Status, NA-ACCORD, 1996–2009

Event	Years	Cumulative Incidence Trend		Cause-Specific Hazard Rate Trend	
		sdHR* (95% CI)	*P* Value	csHR* (95% CI)	*P* Value
Kaposi sarcoma					
HIV-infected	2000-2004	0.63 (0.52-0.77)	<0.001	0.59† (0.48-0.72)	<0.001
	2005-2009	0.61 (0.49-0.76)	<0.001	0.53† (0.43-0.66)	<0.001
Uninfected	–	Too few events to estimate trends	–	Too few events to estimate trends	–
Non-Hodgkin lymphoma					
HIV-infected	2000-2004	0.74† (0.61-0.89)	0.001	0.64 (0.53-0.78)	<0.001
	2005-2009	0.59† (0.49-0.72)	<0.001	0.45 (0.37-0.56)	<0.001
Uninfected	2000-2004	1.29† (0.87-1.92)	0.21	1.23 (0.82-1.82)	0.31
	2005-2009	1.08† (0.73-1.59)	0.71	0.96 (0.65-1.42)	0.84
Lung cancer					
HIV-infected	2000-2004	1.11† (0.88-1.42)	0.38	0.91 (0.71-1.16)	0.44
	2005-2009	1.00† (0.78-1.27)	0.98	0.68 (0.53-0.87)	0.002
Uninfected	2000-2004	0.93† (0.75-1.15)	0.48	0.89 (0.71-1.10)	0.28
	2005-2009	0.68† (0.55-0.84)	<0.001	0.61 (0.49-0.76)	<0.001
Anal cancer					
HIV-infected	2000-2004	1.76 (1.19-2.61)	0.005	1.52 (1.03-2.26)	0.04
	2005-2009	1.96 (1.31-2.93)	0.001	1.50 (1.01-2.24)	0.05
Uninfected	2000-2004	2.05 (0.44-9.51)	0.36	1.97 (0.43-9.11)	0.38
	2005-2009	1.97 (0.44-8.90)	0.38	1.79 (0.40-8.11)	0.45
Colorectal cancer					
HIV-infected	2000-2004	1.83 (1.04-3.20)	0.03	1.53 (0.88-2.68)	0.13
	2005-2009	2.01 (1.16-3.48)	0.01	1.44 (0.83-2.51)	0.19
Uninfected	2000-2004	0.76 (0.59-0.98)	0.03	0.73 (0.57-0.94)	0.02
	2005-2009	0.56 (0.44-0.73)	<0.001	0.52 (0.40-0.66)	<0.001
Liver cancer					
HIV-infected	2000-2004	1.62 (0.99-2.64)	0.05	1.32 (0.81-2.16)	0.26
	2005-2009	2.01 (1.25-3.24)	0.004	1.38 (0.85-2.23)	0.20
Uninfected	2000-2004	1.56 (0.89-2.76)	0.12	1.50 (0.84-2.66)	0.17
	2005-2009	1.67 (0.96-2.91)	0.07	1.51 (0.86-2.64)	0.15
Hodgkin lymphoma					
HIV-infected	2000-2004	0.73 (0.49-1.11)	0.15	0.64 (0.43-0.98)	0.04
	2005-2009	0.79 (0.52-1.20)	0.27	0.61 (0.40-0.94)	0.02
Uninfected	2000-2004	1.74 (0.58-5.22)	0.33	1.66 (0.55-5.01)	0.37
	2005-2009	1.58 (0.53-4.74)	0.42	1.42 (0.48-4.25)	0.53
Melanoma					
HIV-infected	2000-2004	0.73 (0.40-1.34)	0.31	0.64 (0.35-1.17)	0.15
	2005-2009	0.66 (0.36-1.22)	0.19	0.51 (0.27-0.95)	0.03
Uninfected	2000-2004	0.83 (0.60-1.14)	0.25	0.81 (0.59-1.12)	0.21
	2005-2009	0.52 (0.38-0.72)	<0.001	0.49 (0.35-0.68)	<0.001
Oral cavity/pharyngeal cancer					
HIV-infected	2000-2004	1.09 (0.67-1.76)	0.74	0.92 (0.57-1.49)	0.74
	2005-2009	1.27 (0.79-2.03)	0.32	0.93 (0.58-1.49)	0.75
Uninfected	2000-2004	0.96 (0.70-1.32)	0.81	0.93 (0.68-1.27)	0.64
	2005-2009	0.59 (0.43-0.82)	0.002	0.54 (0.39-0.75)	<0.001
Death‡					
HIV-infected	2000-2004	0.68† (0.65-0.70)	<0.001	0.67† (0.65-0.70)	<0.001
	2005-2009	0.42† (0.41-0.44)	<0.001	0.42† (0.41-0.44)	<0.001
Uninfected	2000-2004	0.96† (0.91-1.01)	0.09	0.95† (0.91-1.01)	0.08
	2005-2009	0.80† (0.76-0.84)	<0.001	0.80† (0.76-0.84)	<0.001

csHR = cause-specific hazard ratio; NA-ACCORD = North American AIDS Cohort Collaboration on Research and Design; sdHR = subdistribution hazard ratio.

* sdHR measures calendar changes in cumulative cancer incidence or cumulative all-cause mortality, and csHR measures calendar changes in cancer-specific or mortality-specific hazard rates. Calendar era estimates use 1996–1999 as reference. All estimates adjusted for sex, race, and cohort.

† Evidence of violation of proportional hazards assumption. Estimate should be interpreted as a weighted average over all ages.

‡ Analysis in which melanoma was the competing event.