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Cancer burden attributable to cigarette smoking among HIV-infected people in North America

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Abstract

Objective—With combination-antiretroviral therapy, HIV-infected individuals live longer with an elevated burden of cancer. Given the high prevalence of smoking among HIV-infected populations, we examined the risk of incident cancers attributable to ever smoking cigarettes.

Design—Observational cohort of HIV-infected participants with 270,136 person-years of follow-up in the North American AIDS Cohort Collaboration on Research and Design consortium. Among 52,441 participants; 2306 were diagnosed with cancer during 2000–2015.

Main outcome measures—Estimated hazard ratios (HR) and population-attributable fractions (PAF) associated with ever cigarette smoking for all cancers combined, smoking-related cancers, and cancers that were not attributed to smoking.

Results—People with cancer were more frequently ever smokers (79%) compared to people without cancer (73%). Adjusting for demographic and clinical factors, cigarette smoking was associated with increased risk of cancer overall (HR=1.33 [95% confidence interval: 1.18–1.49]); smoking-related cancers (HR=2.31 [1.80–2.98]), lung cancer (HR=17.80 [5.60–56.63]); but not non-smoking-related cancers (HR=1.12 [0.98–1.28]). Adjusted PAFs associated with ever cigarette smoking were as follows: all cancers combined, PAF=19% [95% confidence interval: 13%–25%]; smoking-related cancers, PAF=50% [39%–59%]; lung cancer, PAF=94% [82%–98%]; and non-smoking-related cancers, PAF=9% [1%–16%].

Conclusions—Among HIV-infected persons, approximately one fifth of all incident cancer, including half of smoking-related cancer, and 94% of lung cancer diagnoses could potentially be prevented by eliminating cigarette smoking. Cigarette smoking could contribute to some cancers that were classified as non-smoking-related cancers in this report. Enhanced smoking cessation efforts targeted to HIV-infected individuals are needed.

Keywords

HIV; Smoking; Cancer; Attributable Risk; North America

Introduction

As the population of effectively treated HIV-infected persons grows, the burden of non-AIDS-defining cancers has increased [1]. The availability of combination antiretroviral therapy (ART) since 1996 has led to a decrease in AIDS incidence and has improved survival after HIV diagnosis [2–7]. With the aging of the HIV-infected population, cancer has emerged as an increasingly important contributor to morbidity and mortality [1,5,7]. An increased risk of cancer among those with HIV is due in part to a high prevalence of cancer risk factors, including tobacco use. In a meta-analysis of 113 studies across developed countries, largely in North America and Western Europe, a large proportion (54%) of HIV-infected people were current smokers [8]. A representative population-based survey of HIV-infected people in care in the United States during 2009 found that 42% were current smokers and another 20% were former smokers [9]. Because this population-based prevalence estimate of current smokers among adults with HIV was twice that for the U.S. general population during the same time [9,10], there is a need to examine health risks from smoking among people living with HIV.

Smoking contributes to the etiology of a range of cancers, including but not limited to cancers of the lung, larynx, liver, colon and rectum, kidney/renal pelvis, and oral cavity, as well as leukemia [11]. Smoking can also contribute to additional cancers for which the etiologic role is less well established [12]. Approximately 29% of all cancer deaths in the overall U.S. population during 2010 were attributable to smoking [13]. Less well defined is the contribution of smoking to the burden of cancer among individuals living with HIV infection and the combined effects of HIV infection and ART with smoking in relation to cancer incidence. In a study of HIV-infected individuals in Denmark, the fraction of cancer diagnoses attributable to smoking was estimated to be 27% for all cancers combined and 91% for smoking-related cancers [14]. A comparable level of cancer mortality was attributed to smoking in an international study of HIV-infected people that included U.S. participants [15]. This present study describes the burden of cancer attributable to cigarette smoking in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), which captures data pertaining to a large HIV-infected population in North America [16], most of whom were followed after initiating ART. Estimates of population-attributable fractions (PAF) were based on the prevalence of ever smoking in the cohort and the hazard ratio for cancer incidence associated with this exposure during follow-up.

Methods

The NA-ACCORD is a consortium of 22 cohort studies of HIV-infected adults in care (≥18 years of age) [16]. Sixteen cohorts (12 clinical and 4 interval) contributed validated cancer diagnoses and smoking data for the present analysis. The human subject research activities of NA-ACCORD and each participating cohort study were reviewed and approved by their respective local institutional review boards and by the Johns Hopkins School of Medicine. Individual cohorts validated cancer diagnoses through medical records, including pathology reports, or through linkage with cancer registries [17].

The 16 cohorts initially included 72,854 patients. For analysis, 34 people less than 18 years of age were excluded. There were 3080 people diagnosed with cancer within 6 months after their study entry date. These people were excluded, as were the 7724 people with follow-up time of less than 6 months. Another 9,575 people with missing smoking status, whose history of smoking could not be imputed because of the absence of the complete set of demographic and clinical variables were also excluded.

Based on these criteria, there were 52,441 HIV-infected patients in the analytic cohort, all of whom were cancer free at study entry. They contributed 270,136 person-years of follow-up. The 50,135 people who remained cancer-free contributed 259,483 person-years. The 2,306 people who were diagnosed with cancer during the study period contributed 10,653 person-years prior to their first cancer diagnoses, at which time follow-up was censored.

Study entry was taken to be the later of six-months after the baseline date when a participant was initially enrolled in the study and the cancer observation start-date, with an administrative censoring date of January 1, 2000. Study exit was defined as the earliest date of first cancer diagnosis, death date, last CD4 or VL measurement plus 1 year, cancer observation stop-date, cohort close date, and December 31, 2015.

Categories of cancer included in analyses were all cancers combined, smoking-related cancers, and non-smoking-related cancers. Cancers of the following anatomic sites, listed in descending order of occurrence in the study population, were considered smoking-related [11,18]: lung (N=214), liver (N=85), colon and rectum (N=77), oral cavity (N=74), kidney/renal pelvis (N=47), cervix (N=43), bladder (N=29), larynx (N=25), leukemia (N=23), pancreas (N=21), esophagus (N=17), and stomach (N=11). In addition to lung cancer, smoking-related cancers other than lung cancer were grouped for analysis. Non-smoking-related cancers included melanoma and non-melanoma skin cancer (N=399), non-Hodgkin lymphoma (N=307), cancer of the anus (N=211), Kaposi sarcoma (N=289),[19] prostate (N=154), Hodgkin lymphoma (N=87), breast (N=78), brain and other nervous system (N=26), myeloma (N=21), thyroid (N=18), testis (N=15), soft tissue (N=11), vulva (N=10), penis (8), and ovary (n=6). In a sensitivity analysis, anal and vulvar cancer were classified as smoking-related.

Information on demographic characteristics, baseline HIV disease markers (CD4 cell count [CD4] and HIV RNA viral load [VL]), ART exposure, and medical comorbidities (hepatitis B virus [HBV] and hepatitis C virus [HCV] infections and stage 4 chronic kidney disease) was obtained from participating cohorts. Cigarette smoking status (time fixed, ever versus never) was available as either observed or imputed data for all 52,441 participants. Observed data on ever versus never smoking status were available for 39,309 subjects (75%) and data on ever versus never smoking status were imputed for 13,132 subjects in the analytic cohort (25%). Data were assembled on the contribution of smoking to the incidence of first cancers for each cohort from electronic medical records, chart reviews, and patient reports. Although survey questionnaires administered to participants in some NA-ACCORD cohort studies included current versus past cigarette smoking history and intensity and duration of smoking, the reduced sample size of patient-reported smoking intensity and duration data precluded their use in the present analysis.

Two-sided Chi-square tests were performed to measure associations between demographic, behavioral and clinical characteristics of individuals and risk of cancer diagnosis (PROC FREQ, SAS version 9.3, Cary, NC). Imputation of ever versus never smoking status was only performed for those people with missing smoking data and complete information for all other demographic and clinical variables in Table 1. Imputation was performed using logistic regression (PROC MI, SAS version 9.3, Cary, NC). Five sets of imputed values provided nearly identical PAF results (data not shown). Results from the first model are presented.

Cox proportional hazard models were used to estimate adjusted hazard ratios (aHR) and 95% confidence intervals (CI) (lower- or upper-bound) associated with ever versus never smoking for specified cancer outcomes (PROC PHREG, SAS). A threshold of $p<0.05$ was used for defining statistical significance. Unadjusted hazard ratios (HR) are presented along with HRs adjusted for age, sex, race (non-white, white, and unknown), HIV risk group (injection drug use [IDU], non-IDU, and other/unknown), AIDS diagnosis at study entry, baseline CD4 count (cells/mm^3: <200, ≥200, and missing), VL (copies/mL: ≤400, >400, and missing), ART versus no ART prior to the baseline date for this study, HBV or HCV infection, and the presence of stage 4 chronic kidney disease. End stage renal disease may only be on the causal pathway between smoking and some cancers. In sensitivity analyses HRs were re-calculated after removing this variable. PAFs were calculated with a SAS macro provided by Laaksonen and colleagues [20]. Because follow-up ended at the time of first cancer diagnosis, all PAF estimates describe the proportional contribution of smoking to the incidence of first cancers. The greater than 200 diagnoses of Kaposi sarcoma, non-Hodgkin lymphoma, and anal cancer provided sufficient numbers to fit adjusted models and present HRs and PAF for these cancers. Although there were 399 melanoma and non-melanoma skin cancer cases in the dataset, PAFs were not estimated for this heterogeneous and unevenly reported subset of malignancies.

Results

The analytic dataset included 52,441 HIV-infected people, of whom 2,306 (4%) were diagnosed with cancer. Median participant follow-up was 3.8 years, interquartile range: 1.5–8.1 years. The incidence rate of all cancer combined during 270,136 person-years was 8.53/1000. Table 1 presents demographic attributes by cancer outcome. A higher proportion of people with cancer than people without cancer diagnoses had ever smoked cigarettes (79% vs. 73%, $p<0.001$). Among people without incident cancer, 73% were classified as ever smokers using observed data and 72% based on imputed data. Among people with incident cancer, 79% with observed and 79% for imputed data were classified as ever smokers.

Compared to individuals without cancer diagnoses, individuals diagnosed with cancer were older ($p<0.001$) at study entry and more frequently male (81% vs. 78%, $p<0.003$). More individuals with a cancer diagnosis than individuals without cancer diagnoses had an AIDS diagnosis at entry (25% vs. 18%, $p<0.001$), and more had started ART before enrollment into NA-ACCORD (56% vs. 49%, $p<0.001$). Excluding 2,955 people with missing values (6%), 30% of individuals with a cancer diagnosis during follow-up had a CD4 count of fewer than 200 cells/mm^3 at entry compared to 24% of subjects without a cancer diagnosis

(p<0.001). HBV infection was more common among individuals with incident cancer than those without a cancer diagnosis (11% vs. 7%, p<0.001), as was the proportion with HCV infection in those with cancer versus those without cancer (23% vs. 18%, p=0.001).

In adjusted analyses, as shown in Table 2, ever smoking cigarettes was associated with an elevated risk for all cancers combined (aHR=1.33 [95% CI: 1.18–1.49]), including smoking-related cancers (aHR=2.31 [1.80–2.98]) but not cancers not classified as smoking-related (aHR=1.12 [0.98–1.28]). Among the smoking-related cancers, the association was strongest for lung cancer (aHR=17.80 [5.60–56.63]) but remained statistically significant for all other smoking-related cancers, excluding lung cancer (aHR=1.59, [1.22–2.06]). The associations with smoking for three other cancers with at least 200 incident cancer events were as follows: Kaposi sarcoma (aHR=1.03, [CI=0.77–1.38]), non-Hodgkin lymphoma (aHR=1.35, [0.98–1.86]), and anal cancer (aHR=1.57, [1.08–2.28]). In sensitivity analyses that removed end stage renal disease from adjusted models, HRs in Table 2 did not change appreciably (data not shown).

Table 2 also presents PAFs for having ever smoked. Unadjusted and adjusted models produced similar PAF estimates. Based on adjusted PAF models, we estimated that 19% [95% CI: 13%–25%] of all cancers were attributable to ever smoking cigarettes, including 50% [39%–59%] of smoking-related cancers and 9% [1%–16%] of other cancers that we did not classify as being attributable to smoking. Almost all lung cancer in this study of HIV-infected individuals, 94% [82%–98%] were attributable to cigarette smoking. The adjusted PAF of having ever smoked for Kaposi's sarcoma, non-Hodgkin lymphoma and anal cancer were 3% [−19%–20%, 22% [2%–38%], and 32% [9%–49%] respectively. Compared to the estimate in Table 2, in a sensitivity analysis that classified anal and vulvar cancers as smoking-related, the adjusted PAF decreased from 50% [39%–59%] to 45% [35%–53%].

Discussion

In our study of HIV-infected individuals treated with ART in North America, almost three-quarters were ever cigarette smokers, consistent with results from prior studies [8,9]. Compared to never smokers, the risk of a smoking-related cancer diagnosis was more than twice as high among those who ever smoked, and the risk of a lung cancer was nearly 18 times as high. Approximately one fifth of cancer diagnoses in this population were potentially attributed to smoking, including 50% of smoking-related cancers and 94% of lung cancer diagnoses. Our findings indicated that a substantial fraction of cancer diagnoses among HIV-infected individuals potentially would not have occurred if they had never smoked.

We estimated that 19% of all cancers were attributed to ever smoking, consistent with the findings in an HIV cohort in Denmark. [14] That study used a more exclusive definition of smoking-related cancers [11,18]. The narrower definition yielded a higher smoking-related cancer PAF compared with our estimate (a 91% PAF for lung, head and neck, esophageal, and bladder cancers versus a 50% PAF based on our broader definition of smoking-related cancers). PAF estimates for smoking and cancer in the general population primarily focus on mortality and are not comparable with our incidence data [14,18]. Our estimate of PAF for

smoking and incident lung cancer is, however, consistent with a recent PAF estimate for cigarette smoking and lung cancer in the general population [21]. One explanation for why the PAF in our HIV population is not substantially higher than in the general population [21] is that Kaposi sarcoma constitutes a non-negligible fraction of all cancers among HIV-infected people, and this type of cancer is not associated with smoking. Because the PAF is a proportional measure, the elevated incidence rate of these cancers attenuates the relative contribution of smoking to the overall cancer burden [22].

Lung cancer is one of the most common cancers in HIV-infected people [23] and as we also found, almost all diagnoses in HIV-infected individuals occur among smokers. [24] HIV infection can have a synergistic effect with tobacco in increasing the risk of this malignancy [25]. Within the lung, smoking suppresses the protective function of pulmonary immunologic defenses, adding to the suppressive effects of HIV on CD4 cell function. Smoking also increases peripheral immune activation, compounding the state of chronic inflammation produced by HIV infection and the risk of lung cancer.

If no one in our HIV-infected study population had ever smoked, we estimate that 9% of non-smoking-related cancers would have been averted. This could be a consequence of smoking in the etiology of some cancers that we did not classify as smoking-related or unmeasured relationships between smoking and other cancer risk factors. Anal cancer was diagnosed at similar frequency to lung cancer and was associated with smoking (aHR=1.57, [1.08–2.28]). References used in this report did not classify anal cancer as a smoking-related cancer. [11,18] Other data link smoking to the pathogenesis of invasive anal cancer, [26–27] with current smokers at highest risk.[27]

In accordance with the 2014 Surgeon General's Report[11] we classified seven leading cancers (N>75) as non-smoking-related cancers: melanoma and non-melanoma skin cancer, non-Hodgkin lymphoma, anal cancer, Kaposi sarcoma, prostate cancer, Hodgkin lymphoma, and breast cancer. We are unaware of studies that show smoking is causal for these cancers among people living with HIV. Because smoking could increase the risk of anogenital malignancies among HIV-infected individuals [28–31], a sensitivity analysis was performed in which anal and vulvar cancers were classified as smoking-related. Compared to smoking-related cancers presented in Table 2, the adjusted PAF for this model was slightly attenuated. A protective effect of smoking on Kaposi sarcoma in a study preceding the ART era [19] was not replicated in this report (i.e., aHR=1.03, [0.77–1.38]), possibly due to confounding with Kaposi sarcoma-related risk factors.

In the United States, the prevalence of smoking among HIV-infected people is substantially higher than in the general population, and most HIV-infected individuals either currently smoke or have previously smoked [9,14,15]. As ART has increasingly made HIV a chronic disease with decreasing AIDS-related mortality [2–7], there is a rising burden of non-communicable diseases [1–7], including smoking-related cancers [15].

In the SMART trial, with 5,472 HIV-infected people in 33 countries, 24% of all deaths in HIV-infected individuals were attributed to smoking, as were 25% of cardiovascular disease (CVD) events, 25% of bacterial pneumonia episodes, and 31% of non-AIDS-related cancers

[15]. Smoking among HIV-infected people increases the risk of death due to other causes through a combination of mechanisms, including as a driver of metabolic abnormalities among both ART-naïve patients [32] and patients receiving ART [33,34]. Tobacco use in the presence of HIV infection also increases CVD risk [35] and reduces life expectancy [36]. Thus, smoking-associated CVD is a prevalent and preventable cause of morbidity and mortality among people living with HIV infection, adding to our findings with respect to smoking and cancer. Although this study does not directly address the benefits of smoking cessation, because individuals who quit smoking remain in the "ever smoked" group, the high prevalence of smoking in this and other studies of people living with HIV [9,14,15] clearly indicate a need for efforts to encourage smoking cessation in this patient population [36,37].

The substantial fraction of preventable cancers and elevated prevalence of smoking among HIV-infected individuals [8–10] warrants prioritized behavioral and pharmacologic smoking prevention and cessation interventions for this population [38,39]. Although duration of smoking was not considered in the present report on individuals infected with HIV, quitting smoking reduces the risk of cancer, including lung cancer, in the general population [11]. Since many HIV-infected smokers are motivated to quit, health care providers can assist HIV-infected people with smoking cessation at repeated clinical encounters by offering behavioral and pharmacologic interventions. High-quality resources exist specifically to assist HIV care providers in helping their patients to quit smoking [40,41]. In addition to behavioral modalities, which can have variable results depending on the frequency of therapy and patient literacy, pharmacologic interventions (e.g., bupropion, varenicline, nicotine substitution) are widely available and effective and have few reported interactions with ART.

Strengths of our study include the large representative cohort of HIV-infected people in North America with validated cancer diagnoses and smoking information. NA-ACCORD [16,17] is well suited for studies of HIV-related comorbidities because of the high uptake of ART compared with other studies [2–7]. Lack of details on smoking is the major limitation. It is unclear whether the listed factors are major confounders, but to the extent they are, our estimates would be biased. Imputed smoking prevalence was unlikely to affect results since imputed and observed data were similar for people with and those without cancer. No substantial confounding of the association between smoking and cancer was observed in models adjusted for the factors that we considered, but potential confounding by unmeasured factors, such as secondhand smoke, [8] and human papillomavirus infection status [25–29], cannot be dismissed. Our study did not adjust for alcohol use and marijuana and crack-cocaine smoking, which increase the risk of certain cancers, or incorporate updated values of HIV disease markers.

In conclusion, the prevalence of ever cigarette smoking in this HIV cohort study was estimated at 73%, and 19% of all incident cancers were attributed to smoking, including 50% of cancers previously defined as smoking-related and 94% of lung cancer diagnoses. These findings provide insight into the considerable cancer burden attributable to cigarette smoking among HIV-infected people and indicate a need for effective smoking cession programs for HIV-infected individuals [21,36,37].

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Table 1

Characteristics of adults with HIV, and with and without cancer diagnosis during follow-up, North American-AIDS Cohort Collaboration on Research and Design

		Patients with a Cancer Diagnosis During Follow-up		Patients with No Cancer Diagnosis During Follow-up		P-value	All Patients	
Characteristic		**No.**	**%**		**%**		**No.**	**%**
Total		2,306	4%	50,135	96%		52,441	100%
Smoking Status								
	Never	485	21%	13,462	27%	<0.001	13,947	27%
	Ever	1,821	79%	36,673	73%		38,494	73%
Age at Entry (Years)								
	18–39	707	31%	25,030	50%	<0.001	25,797	49%
	40–49	877	38%	16,976	34%		17,853	34%
	50–59	539	23%	6689	13%		7,228	14%
	60+	183	8%	1440	3%		1,623	3%
Sex								
	Female	445	19%	10,989	22%	0.003	11,434	22%
	Male	1,861	81%	39,146	78%		41,007	78%
HIV Transmission Risk Category								
	No IDU	1,853	80%	40,212	80%	0.07	42,065	80%
	IDU	272	12%	5405	11%		5,677	11%
	Other/Unknown	181	8%	4518	8%		4,699	9%
Race								
	Non-White	912	40%	22,991	46%	<0.001	23,903	46%
	White	1,303	57%	23,030	46%		24,333	46%
	Unknown	91	4%	4114	8%		4,205	8%
AIDS-defining illness								
	No	1,737	75%	41,090	82%	<0.001	42,827	82%
	Yes	569	25%	9045	18%		9,614	18%
ART use								

		Patients with a Cancer Diagnosis During Follow-up		Patients with No Cancer Diagnosis During Follow-up		P-value	All Patients	
Characteristic		**No.**	**%**		**%**		**No.**	**%**
	No	1,013	44%	25,761	51%	<0.001	26,774	51%
	Yes	1,293	56%	24,374	49%		25,667	49%
CD4 Cell Count (cells/mm^3)								
	<200	3674	29%	11,153	22%	<0.001	11,827	23%
	≥200	1,524	66%	36,135	72%		37,659	72%
	Missing	108	5%	2847	6%		2,955	6%
HIV RNA (copies/mL)								
	≤400	775	34%	17,854	36%	0.06	18,629	36%
	>400	1,338	58%	27,846	56%		26,184	56%
	Missing	193	8%	4435	9%		4,628	9%
Hepatitis B Infection								
	No	2,052	89%	46,456	93%	<0.001	48,508	93%
	Yes	254	11%	3679	7%		3,933	7%
Hepatitis C Infection								
	No	1,787	77%	40,910	82%	<0.001	42,697	81%
	Yes	519	23%	9225	18%		9,744	19%
Stage 4 Chronic Kidney Disease								
	No	2,250	98%	49,404	99%	<0.001	33,300	98%
	Yes	56	2%	731	1%		787	2%

Abbreviations:

Footnotes:

Sex, race, and HIV transmission risk were measured at enrollment into the NA-ACCORD.

Smoking status was measured as ever having evidence of cigarette smoking while under observation in the NA-ACCORD. Participants from cohorts with incomplete smoking status were imputed. Hepatitis C infection was measured as a) positive hepatitis C antibody; OR b) detectable hepatitis C RNA; OR c) hepatitis C genotype result at any time while under NA-ACCORD observation. Hepatitis B infection was measured as a) positive hepatitis B surface antigen; OR b) positive hepatitis B E antigen; OR c) detectable hepatitis B DNA at any time while under NA-ACCORD observation. CD4 count and HIV RNA were measured as close to study entry as possible, within the window of prior to, to 6 months after, study entry.

AIDS-defining illness was defined by International Classification of Diseases Ninth Edition, (ICD-9) codes for AIDS-defining illnesses, including: pneumocystis pneumonia, tuberculosis, mycobacterium, cytomegalovirus, HIV wasting, HIV dementia, candidiasis, cryptococcosis, toxoplasmosis of the brain, coccidioidomycosis, histoplasmosis, isosporiasis, herpes zoster, herpes simplex, bacterial pneumonia, history of clinical AIDS diagnosis was measured at, or prior to, study entry. HAART use was defined as HAART prescription at or before study entry.

Stage 4 chronic kidney disease was measured as estimated glomerular filtration rate (eGFR), calculated using the Chronic Kidney Disease Epidemiology Collaboration, or CKD-EPI, equation) <30 (the first date of recorded eGFR <30 was the date from which an individual was classified as having CKD stage 4), measured within the window of prior to, or within 9 months after, study entry. Those without a single creatinine measurement are classified as missing. ART, antiretroviral therapy; IDU, injection drug use; No., number.

Table 2

Hazard Ratios and Population Attributable Fractions for Cancer Associated With Ever Smoking Cigarettes

			Hazard Ratios Associated With Ever Smoking Cigarettes				Population-Attributable Fractions Associated With Ever Smoking Cigarettes			
Cancer Diagnosis	**No.**	**Cigarette Smoking Prevalence, Subjects Diagnosed with Cancer**	**HR**	**95% CI**	**aHR***	**95% CI**	**PAF**	**95% CI**	**aPAF***	**95% CI**
All Cancers Combined	2,306	79%	1.41	[1.26, 1.58]	1.33	[1.18, 1.49]	22%	[15%, 27%]	19%	13%, 25%]
Smoking-Related	666	88%	2.65	[2.07, 3.39]	2.31	[1.80, 2.98]	54%	[43%, 62%]	50%	[39%, 59%]
Lung Cancer	214	99%	21.73	[6.87, 68.71]	17.80	[5.60, 56.63]	95%	[84%, 98%]	94%	[82%, 98%]
Smoking-Related, Excluding Lung Cancer	452	83%	1.77	[1.37, 2.28]	1.59	[1.22, 2.06]	35%	[20%, 47%]	31%	[16%, 44%]
Not Smoking-Related	1,640	75%	1.16	[1.02, 1.32]	1.12	[0.98, 1.28]	10%	[2%, 17%]	9%	[1%, 16%]
Kaposi’s sarcoma	289	74%	1.07	[0.81, 1.41]	1.03	[0.77, 1.38]	5%	[−15%, 22%]	3%	[−19%, 20%]
Non-Hodgkin Lymphoma	307	79%	1.45	[1.06, 1.98]	1.35	[0.98, 1.86]	25%	[7%, 40%]	22%	[2%, 38%]
Anal cancer	211	82%	1.60	[1.11, 2.30]	1.57	[1.08, 2.28]	33%	[11%, 49%]	32%	[9%, 49%]

aHR, adjusted HR; aPAF, adjusted PAF; ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; NA-ACCORD, North American-AIDS Cohort Collaboration on Research and Design; No., number; PAF, population-attributable fraction.

*Hazard ratios were adjusted for age, sex, race, HIV risk group, hepatitis B and hepatitis C infections, baseline CD4 cell count and HIV RNA level, AIDS diagnosis at baseline, ART use prior to enrollment in NA-ACCORD, and stage 4 chronic kidney disease.