VOLUME 36 · NUMBER 1 · JANUARY 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Anal Cancer Risk Among People With HIV Infection in the United States

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Published at jco.org on November 15, 2017.

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0732-183X/18/3601w-68w/$20.00

ABSTRACT

Purpose
People with HIV infection have an elevated risk of anal cancer. However, recent calendar trends are incompletely described, and which population subgroups might benefit from cancer screening is unknown.

Methods
We used linked data from HIV and cancer registries in nine US areas (1996 to 2012). We calculated standardized incidence ratios to compare anal cancer incidence in people with HIV infection with the general population, used Poisson regression to evaluate anal cancer incidence among subgroups of people with HIV and to assess temporal trends, and estimated the cumulative incidence of anal cancer to measure absolute risk.

Results
Among 447,953 people with HIV infection, anal cancer incidence was much higher than in the general population (standardized incidence ratio, 19.1; 95% CI, 18.1 to 20.0). Anal cancer incidence was highest among men who have sex with men (MSM), increased with age, and was higher in people with AIDS than in those without AIDS (ie, HIV only; adjusted incidence rate ratio, 3.82; 95% CI, 3.27 to 4.46). Incidence among people with HIV increased steeply during 1996 to 2000 (annual percentage change, 32.8%; 95% CI, −1.0% to 78.2%), reached a plateau during 2001 to 2008, and declined during 2008 to 2012 (annual percentage change, −7.2%; 95% CI, −14.4% to 0.6%). Cumulative incidence after a 5-year period was high for MSM with HIV only age 45 to 59 or ≥ 60 years (0.32% to 0.33%) and MSM with AIDS age 30 to 44, 45 to 59, or ≥ 60 years (0.29% to 0.65%).

Conclusion
Anal cancer incidence is markedly elevated among people with HIV infection, especially in MSM, older individuals, and people with AIDS. Recent declines may reflect delayed benefits of HIV treatment. Groups with high cumulative incidence of anal cancer may benefit from screening.

J Clin Oncol 36:68-75. © 2017 by American Society of Clinical Oncology

INTRODUCTION

The risk of human papillomavirus (HPV)–associated cancers increases with immunosuppression.[1-3] People with advanced HIV disease (ie, AIDS) have an elevated risk for in situ and invasive HPV-associated cancers, including anal cancer.[3] This elevated risk is consistent with a high incidence and persistence of anal HPV infection among individuals with HIV infection.[3,4] Anal cancer risk associated with HIV infection is particularly high among men who have sex with men (MSM),[5] with an estimated 37-fold increased risk compared with the general population.[6]

Given their high risk for anal cancer, men with HIV (especially MSM) make up a major fraction of people diagnosed with anal cancer in the United States.[7,8] The availability of highly active antiretroviral therapy (HAART) for HIV infection since 1996 has been associated with improved immune function and declining incidence of some virus-related cancers, such as Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer.[9] In contrast, anal cancer incidence in people with HIV infection may be increasing in the United States and elsewhere.[9-11] Among these individuals, a low CD4 count is associated with an increased risk of anal cancer,[12,13] and immunosuppression seems most important at early stages in the development of anal cancer.[14] Although anal cancer incidence did not clearly decline during the first decade of the HAART era, a lag might have been possible, and so the impact of HAART on anal cancer trends might take longer to see.[3]

ASSOCIATED CONTENT

Appendix
DOI: https://doi.org/10.1200/JCO.2017.74.9291

DOI: https://doi.org/10.1200/JCO.2017.74.9291

Anal cytology screening can detect precancerous anal lesions, including high-grade squamous intraepithelial lesions [HSILs], and invasive cancers while they are still at a localized stage, but no established screening guidelines for clinical practice exist.[5,15] From a public health perspective, to best target screening, insight can be gained from assessing the cumulative incidence of anal cancer for various population subgroups defined, for example, by HIV risk group, age, and immune status. Cumulative incidence (also referred to as absolute risk) is the probability of developing anal cancer in the presence of competing mortality. It depends on the incidence rate of anal cancer and on survival because to be at risk for cancer at a given time, one must first survive to that time. Accounting for competing mortality is especially important in populations with high mortality, such as people with HIV infection, to characterize the absolute risk of anal cancer accurately.

We quantified the risk of anal cancer among people with HIV infection in the United States during 1996 to 2012, by examining the associations of anal cancer incidence with demographic characteristics and prior AIDS diagnosis, and we assessed temporal trends. We also provide estimates of the cumulative incidence of anal cancer among subgroups of individuals with HIV with and without AIDS.

METHODS

The HIV/AIDS Cancer Match Study incorporates linked data collected by US HIV and cancer registries.[16] The study was approved by institutional review boards at participating registries.

This study evaluated a cohort of people with HIV infection identified in HIV registries from eight US states and Puerto Rico. For each registry, follow-up for each individual started 3 months after the latest of the following: beginning of systematic name-based state HIV registration; 3 months after HIV report date (or AIDS diagnosis if this was earlier); start of cancer registration; or January 1, 1996. Follow-up ended at the earliest of anal cancer diagnosis, death, or end of cancer registry coverage; the last date of follow-up was December 31, 2012. Diagnoses of invasive anal cancer were identified through linkage with the cancer registries.

We calculated anal cancer incidence rates (observed patients with cancer per 100,000 person-years) and standardized incidence ratios (SIRs) defined as the observed number of patients with cancer divided by the expected number of patients with cancer, where expected counts were estimated by applying general population cancer incidence rates to person-time in the HIV population on the basis of sex, age, race/ethnicity, calendar year, and cancer registry. We used Poisson regression to estimate incidence rate ratios (IRRs) to compare anal cancer incidence in subgroups of individuals with HIV infection. Multivariable models included sex and HIV risk group reported in the HIV registries (for males: MSM, injection drug users [IDUs], men who were both MSM and IDUs, heterosexual, other/unknown; for females: IDUs, heterosexual, other/unknown), attained age-group (< 30, 30 to 44, 45 to 59, ≥ 60 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic), attained calendar period (1996 to 2000, 2001 to 2004, 2005 to 2008, 2009 to 2012), prior AIDS diagnosis (time updated: AIDS *v* no AIDS [ie, HIV only]), and registry area. We conducted similar stratified analyses separately for MSM, other males, and females.

We evaluated time trends and changes in the slope of anal cancer incidence, fitted under a log-linear model, by using Joinpoint software (https://surveillance.cancer.gov/joinpoint). These models characterize slope estimates as annual percentage changes (APCs) for each calendar year segment. Because registries cover varying calendar periods, in a sensitivity analysis, we assessed the robustness of these findings by conducting analyses separately for registries that provide data starting before 1999 and those that entered later.

We also assessed the cumulative incidence of anal cancer among people with HIV infection separately for those with AIDS versus HIV only, stratified by risk group (MSM, other males, females) and age at AIDS diagnosis (for people with AIDS) or age at HIV report (for people with HIV only). We calculated nonparametric cumulative incidence curves for anal cancer by treating death as a competing event.[17] These curves measure risk from HIV report or AIDS diagnosis. Our cumulative incidence estimates for people with HIV only ignored the onset of AIDS because the future timing of AIDS would be unknown for people with HIV only when they are assessed for possible screening. Because anal cancer incidence was lower before 2000, we started follow-up time for these analyses on January 1, 2000, to obtain estimates that more accurately reflect current risk. The cumulative incidence curves incorporate delayed entry for individuals whose follow-up started later because of the left truncation of follow-up time before 2000 or before the start of cancer registry coverage. We also estimated the cumulative incidence of anal cancer for MSM with HIV reported or AIDS diagnosed in 1996 to 2000 versus 2009 to 2012. Pointwise CIs were derived for cumulative incidence estimates at 5 and 10 years of follow-up. Analyses not performed with Joinpoint were performed with STATA/SE 14 (StataCorp, Cary, NC) or R version 3.3.2 (https://cran.r-project.org/bin/windows/base/old/3.3.2) statistical software.

RESULTS

The study included 447,953 people with HIV infection followed in the United States during 1996 to 2012. During 3.1 million person-years of observation (median follow-up, 6.5 years), anal cancer was diagnosed in 1,567 patients. Most were observed among MSM (65.0%), patients age 45 to 59 years (51.6%), non-Hispanic black (40.8%) or white (39.2%), and patients with a prior AIDS diagnosis (88.1%) (Table 1).

Anal cancer incidence was substantially elevated among people with HIV infection compared with the general population (SIR, 19.1; 95% CI, 18.1 to 20.0) and among all subgroups of the HIV population (Table 1). SIRs reflect large increases in incidence relative to the general population and were especially high for the MSM (range, 33.2 to 38.7), younger than age 45 years (range, 29.5-72.4), white (SIR, 37.9), and AIDS diagnosis (SIR, 24.2) groups.

Adjusted IRRs showed that MSM had the highest incidence of anal cancer, and compared with them, incidence was lower in other males (range, 0.32 to 0.38) and females (range, 0.21 to 0.38). Anal cancer incidence increased with age and was highest in whites. AIDS diagnosis was associated with close to a fourfold increased incidence of anal cancer (adjusted IRR, 3.82) compared with HIV only.

Calendar trends during 1996 to 2012 are listed in Table 1 and shown in Figure 1. Two joinpoints were identified in 2000 and 2008, which indicated significant changes in the slope. Incidence increased steeply during 1996 to 2000 (APC, 32.8%; 95% CI, −1.0% to 78.2%), reached a plateau for 2001 to 2008 (APC, 1.4%; 95% CI, −2.6% to 5.6%), and then declined during 2008 to 2012 (APC, −7.2%; 95% CI, −14.4% to 0.6%). As shown in Appendix Figure A1 (online only), this overall pattern was consistent with results in two subsets of participating registry areas. Specifically, within the three registry areas that provided data before 1999, an increase was seen until 2002 followed by a subsequent flat or decreasing trend in incidence. In the six registry areas for which data on anal cancer incidence started later, a flat or decreasing trend was observed from 1999 onward. In comparison,

Table 1. Incidence of Anal Cancer Among People With HIV Infection in the United States, 1996 to 2012

Category	Observed Anal Cancer Cases in People With HIV, No.	SIR (95% CI)	Incidence Rate Per 100,000 Person-Years (%)	Adjusted IRR* (95% CI)	*P**
Overall	1,567	19.1 (18.1 to 20.0)	50.7	—	—
Sex/risk group					< .001
MSM	895	38.7 (36.3 to 41.4)	89.0	Reference	
MSM IDU	122	33.2 (27.6 to 39.7)	86.3	0.92 (0.76 to 1.12)	
Male IDU	148	9.4 (7.9 to 11.0)	32.5	0.32 (0.27 to 0.39)	
Male heterosexual	10	11.4 (5.5 to 20.9)	34.7	0.38 (0.20 to 0.70)	
Male other/unknown	176	10.0 (8.6 to 11.6)	31.2	0.37 (0.32 to 0.44)	
Female IDU	82	13.5 (10.7 to 16.7)	35.6	0.38 (0.30 to 0.47)	
Female heterosexual	18	7.9 (4.7 to 12.4)	18.6	0.21 (0.13 to 0.34)	
Female other/unknown	116	9.0 (7.5 to 10.8)	20.5	0.28 (0.23 to 0.34)	
Age, years					< .001
< 30	28	72.4 (47.7 to 103.8)	10.0	0.31 (0.21 to 0.46)	
30-44	593	29.5 (27.2 to 32.0)	45.8	Reference	
45-59	808	16.2 (15.0 to 17.3)	63.0	1.33 (1.19 to 1.48)	
≥ 60	138	11.8 (9.9 to 13.9)	59.9	1.28 (1.06 to 1.55)	
Race/ethnicity					< .001
White	614	37.9 (35.0 to 41.0)	80.3	Reference	
Black	640	13.6 (12.6 to 14.7)	43.8	0.85 (0.75 to 0.96)	
Hispanic	313	16.4 (14.6 to 18.3)	36.2	0.64 (0.55 to 0.75)	
Prior AIDS diagnosis					< .001
No	186	7.4 (6.4 to 8.6)	16.7	Reference	
Yes	1,381	24.2 (22.9 to 25.5)	70.0	3.82 (3.27 to 4.46)	
Calendar year					.002
1996-2000	79	28.6 (22.6 to 35.6)	36.3	0.65 (0.51 to 0.84)	
2001-2004	374	25.5 (23.0 to 28.2)	53.9	Reference	
2005-2008	582	20.2 (18.6 to 22.0)	54.4	1.03 (0.90 to 1.18)	
2009-2012	532	14.8 (13.5 to 16.1)	48.1	0.98 (0.85 to 1.13)	

NOTE. HIV and cancer registries contributed the following calendar years of follow-up: Colorado (1996 to 2007), Connecticut (2005 to 2010), Georgia (2004 to 2012), Maryland (2008 to 2012), Michigan (1996 to 2010), New Jersey (1996 to 2012), New York (2001 to 2012), Puerto Rico (2003 to 2012), and Texas (1999 to 2009).
Abbreviations: IDU, injection drug user; IRR, incidence rate ratio; MSM, men who have sex with men; SIR, standardized incidence ratio.
*IRRs and *P* values are from a Poisson regression model. Each association is mutually adjusted for the other characteristics in the table and for registry area (data not shown). *P* values are for heterogeneity, except for age where the *P* value is for trend.

incidence in the general population was much lower and showed a steady increase over time. As a result of the calendar trends in the observed and expected incidence of anal cancer, SIRs for anal cancer were highest before 2005 and then declined over time.

Table 2 lists anal cancer incidence rates for the three major sex/risk groups. Overall incidence was 88.7 per 100,000 person-years for MSM, 31.9 per 100,000 person-years for other males, and 24.2 per 100,000 person-years for females. Within each group, patterns largely mirrored those listed in Table 1. Specifically, anal cancer incidence increased with age and was lower in blacks and Hispanics than in whites, although not all IRRs were significant. In all sex/risk groups, a three- to fourfold increased risk was observed in the AIDS diagnosis group compared with the HIV only group.

A total of 279,055 people with AIDS and 220,314 people with HIV only contributed follow-up data in 2000 to 2012 for the cumulative incidence estimates. Cumulative incidence was generally

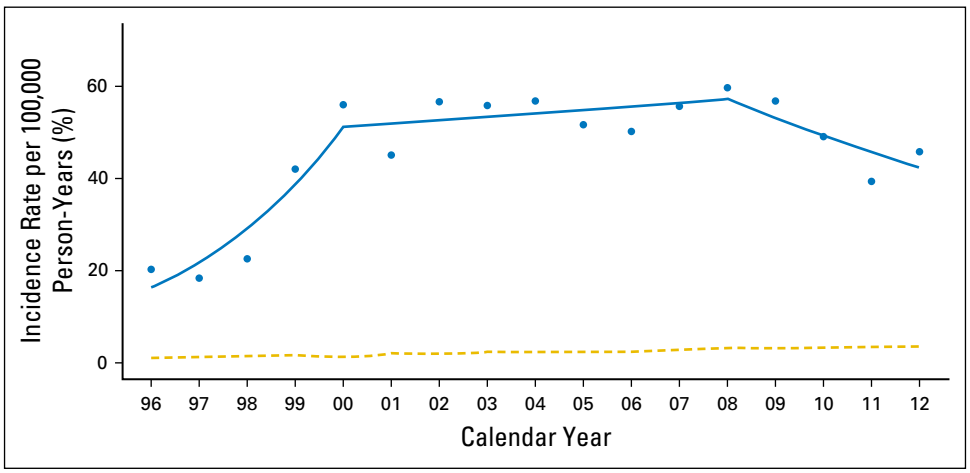

Fig 1. Trend in anal cancer incidence among people with HIV infection and the general population in the United States, 1996 to 2012. Dots indicate the observed incidence of anal cancer among people with HIV in the study population as a function of calendar year. The solid line is the model fitted by Joinpoint, with changes in slope for the incidence trend indicated in 2000 and 2008. The dashed line is the expected incidence in the general population standardized to reflect the demographic characteristics of the HIV population.

Table 2. Incidence of Anal Cancer Among People With HIV Infection Estimated Separately for Sex/Risk Group in Stratified Analyses

Category	Incidence Rate Per 100,000 Person-Years			Adjusted IRR* (95% CI)		
	MSM	Other Males	Females	MSM	Other Males	Females
Overall	88.7	31.9	24.2	—	—	—
Age, years						
< 30	19.5	2.8	5.7	0.35 (0.23 to 0.56)	0.12 (0.03 to 0.48)	0.36 (0.15 to 0.82)
30-44	74.7	30.0	20.0	Reference	Reference	Reference
45-59	115.9	37.7	33.6	1.40 (1.22 to 1.60)	1.06 (0.83 to 1.35)	1.45 (1.08 to 1.94)
≥ 60	131.6	29.6	31.0	1.52 (1.20 to 1.92)	0.80 (0.53 to 1.20)	1.29 (0.77 to 2.17)
Race/ethnicity						
White	102.7	49.0	28.9	Reference	Reference	Reference
Black	90.9	32.5	20.9	0.96 (0.83 to 1.10)	0.65 (0.50 to 0.85)	0.70 (0.47 to 1.02)
Hispanic	60.0	23.1	29.0	0.60 (0.50 to 0.72)	0.43 (0.32 to 0.59)	0.90 (0.60 to 1.36)
Prior AIDS diagnosis						
No	29.3	9.3	9.3	Reference	Reference	Reference
Yes	122.2	42.9	34.1	3.76 (3.10 to 4.55)	4.42 (3.07 to 6.38)	3.25 (2.24 to 4.72)
Calendar year						
1996-2000	75.2	11.5	3.5	0.84 (0.64 to 1.09)	0.40 (0.19 to 0.82)	0.18 (0.04 to 0.75)
2001-2004	98.1	31.5	23.6	Reference	Reference	Reference
2005-2008	93.3	36.1	24.4	0.98 (0.83 to 1.14)	1.21 (0.91 to 1.61)	1.02 (0.71 to 1.48)
2009-2012	80.9	31.9	27.8	0.86 (0.72 to 1.02)	1.12 (0.84 to 1.50)	1.14 (0.79 to 1.63)

NOTE. MSM category includes both MSM categories from Table 1. Abbreviations: IRR, incidence rate ratio; MSM, men who have sex with men.
*IRRs are mutually adjusted for the other characteristics in the table and for registry area (data not shown). Analyses are conducted separately for MSM, other males, and females.

higher in people with AIDS than in those with HIV only, among MSM than other males or females, and among older individuals (Fig 2; Table 3). In most strata, cumulative incidence of anal cancer was < 0.20% at 5 years of follow-up (Table 3). The only strata with a cumulative incidence of at least 0.25% at 5 years were MSM with AIDS who were 30 to 44, 45 to 59, or ≥ 60 years old (cumulative incidence, 0.29% to 0.65%) and MSM with HIV only who were 45 to 59 or ≥ 60 years old (cumulative incidence, 0.32% to 0.33%). As shown in Figure 3, cumulative incidence of anal cancer among MSM with AIDS was similar in the most recent calendar period (2009 to 2012) compared with 1996 to 2000 but with a suggested decline for MSM with HIV only.

DISCUSSION

This study provides information on anal cancer risk in the US HIV population during the HAART era (1996 to 2012). We demonstrate a substantially elevated incidence of anal cancer among people with HIV infection overall. Incidence was greatest among MSM, older age-groups, and individuals with an AIDS diagnosis. Of note, we document a plateau in incidence during 2000 to 2008 and an apparent decline among people with HIV after 2008.

Anal cancer, similarly to cervical cancer, is caused by persistent HPV infection.[18] HPV 16 is the most prevalent type associated with anal cancer and precancerous lesions; HPV 18 is the second most common type in invasive cancers,[19] with important contributions also made by HPV 33 and HPV 39.[20] Elevated risk of anal cancer among people with HIV partly reflects the high prevalence of risky sexual behaviors, especially receptive anal intercourse among MSM, leading to acquisition of anal HPV infection. Tobacco also may act as a cofactor for the development of anal cancer,[21,22] and tobacco use is frequent among people with HIV who live in the United States.[23]

Substantial evidence links HIV-associated immunosuppression to the etiology of anal cancer. HIV infection is associated with prolonged persistence and decreased clearance of anal HPV infection.[24,25] In the current study, anal cancer incidence was almost fourfold higher in people with AIDS than in those with less-advanced disease (ie, HIV only). In a large French cohort study of people with HIV, anal cancer incidence increased with duration of time individuals spent with a low CD4 count and poorly controlled HIV infection.[12] A Swiss case-control study of anal cancer among individuals with HIV also demonstrated that a low CD4 count was a risk factor, especially when documented 6 to 7 years before selection.[13] Finally, anal cancer incidence is substantially elevated among solid organ transplantation recipients, another immunosuppressed population.[26,27]

Because of these associations between immunosuppression and risk of anal cancer, why the incidence of anal cancer has not declined among people with HIV infection after introduction of HAART in 1996 has been difficult to understand. Earlier analytic efforts that used HIV/AIDS Cancer Match Study data available through 2010 actually found an increase over time.[9] However, the current analysis of updated data suggests that the increase in anal cancer incidence was limited to the earlier years and was followed by a plateau. Furthermore, an apparent decrease occurred after 2008 (Fig 1), although the decline is not statistically significant.

This overall pattern could reflect that immunosuppression is especially important at the early stages of anal carcinogenesis related to impaired clearance of HPV or early preneoplastic lesions. Under such a model there would be a lag in the relationship between immunosuppression and the development of cancer, and the population benefits of HAART with respect to a reduction in the incidence of invasive anal cancer, therefore, would be delayed. Finally, anal cancer incidence rose steadily in the general population during 1997 to 2012.[7,9] As a result, a strong decline in anal cancer incidence in people with HIV infection relative to the

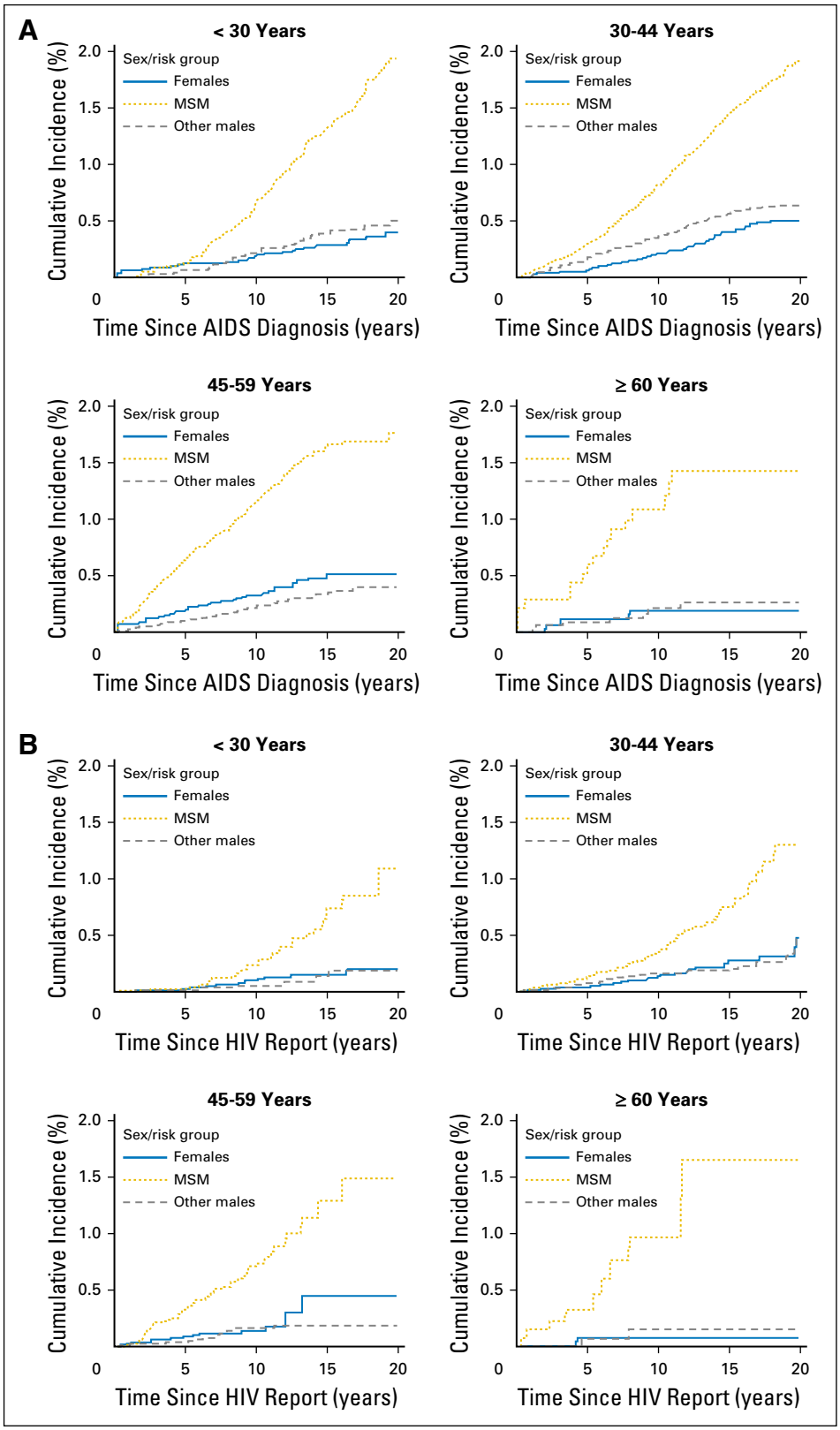

Fig 2. Cumulative incidence of anal cancer in people with HIV infection in the United States. Cumulative incidence of anal cancer among (A) people with AIDS and (B) people with HIV only as a function of follow-up time. Each panel of (A) and (B) presents results for a different age-group as assessed at AIDS diagnosis (for people with AIDS) or HIV report (for people with HIV only). MSM, men who have sex with men.

general population is seen as captured by the SIR, although the SIR remains substantially elevated even in the most recent calendar period.

Anal cancer incidence increased with age in the HIV population, but SIRs were notably higher among younger individuals with HIV infection. These higher SIR estimates may reflect the

Table 3. Five- and 10-Year Cumulative Incidence of Anal Cancer Among People With an AIDS Diagnosis or HIV Only

Sex/Risk Group Stratified by Age*	Cumulative Incidence, % (95% CI)			
	AIDS, 5 Years	AIDS, 10 Years	HIV Only, 5 Years	HIV Only, 10 Years
MSM				
< 30	0.12 (0.05 to 0.19)	0.67 (0.51 to 0.83)	0.02 (0.00 to 0.05)	0.24 (0.12 to 0.35)
30-44	0.29 (0.23 to 0.36)	0.82 (0.72 to 0.91)	0.12 (0.08 to 0.16)	0.34 (0.26 to 0.42)
45-59	0.65 (0.49 to 0.81)	1.14 (0.94 to 1.35)	0.33 (0.22 to 0.44)	0.71 (0.50 to 0.91)
≥ 60	0.52 (0.01 to 1.02)	1.08 (0.42 to 1.73)	0.32 (0.00 to 0.64)	0.95 (0.25 to 1.65)
Other males				
< 30	0.06 (0.00 to 0.12)	0.21 (0.10 to 0.33)	0.01 (0.00 to 0.03)	0.05 (0.00 to 0.11)
30-44	0.16 (0.10 to 0.21)	0.35 (0.28 to 0.42)	0.07 (0.04 to 0.11)	0.16 (0.10 to 0.22)
45-59	0.10 (0.05 to 0.14)	0.21 (0.15 to 0.28)	0.04 (0.01 to 0.07)	0.15 (0.08 to 0.23)
≥ 60	0.09 (0.00 to 0.19)	0.20 (0.04 to 0.37)	0.06 (0.00 to 0.17)	0.15 (0.00 to 0.36)
Females				
< 30	0.12 (0.02 to 0.22)	0.20 (0.08 to 0.31)	0.02 (0.00 to 0.05)	0.09 (0.03 to 0.15)
30-44	0.06 (0.03 to 0.09)	0.21 (0.15 to 0.26)	0.04 (0.02 to 0.06)	0.13 (0.08 to 0.19)
45-59	0.20 (0.11 to 0.29)	0.32 (0.20 to 0.43)	0.08 (0.03 to 0.13)	0.13 (0.05 to 0.21)
≥ 60	0.11 (0.00 to 0.26)	0.18 (0.00 to 0.39)	0.08 (0.00 to 0.23)	0.08 (0.00 to 0.23)

Abbreviation: MSM, men who have sex with men.
*Age is in years and was measured at AIDS diagnosis (for people with AIDS) or HIV report (for people with HIV only). Cumulative incidence estimates for people with HIV only do not censor at the onset of AIDS (see Methods).

relatively strong biologic effect of HIV-associated immunosuppression in accelerating carcinogenesis at younger ages, whereas older individuals have greater opportunity to progress to cancer through additional mechanisms even in the absence of immunosuppression. Non-Hispanic whites had a higher incidence of anal cancer than non-Hispanic blacks or Hispanics, especially among other males than MSM, although the reason is unclear.

Our estimates of the cumulative incidence of anal cancer can provide perspective about the utility of anal cancer screening. In the United States, all individuals age 50 to 75 years are recommended to receive colorectal cancer screening,[28] and although controversy exists about the optimal age to start, the American Cancer Society recommends that all women age 45 to 69 years receive mammography screening for breast cancer.[29] In the general US population during 2011 to 2013, the 5-year cumulative incidence of colorectal cancer for people age 50 years was approximately 0.27%, and for 45-year-old women, the 5-year cumulative incidence of breast cancer was 0.89%.[30] On the basis of these comparisons, one might choose a 5-year cumulative incidence of cancer of 0.25% as the lower limit to target candidate populations for anal cancer screening. Among the people with HIV infection studied here, this threshold was reached for anal cancer only among MSM, specifically those with AIDS beginning at age ≥ 30 years and those with HIV only at age ≥ 45 years.

Thus, the current results suggest that any programs to screen for anal cancer among people with HIV infection would be focused most effectively on certain high-risk subgroups. As shown by the much higher cumulative incidence estimates for MSM with AIDS, screening might start more than a decade later for MSM with HIV only than for those with AIDS. Our cumulative incidence estimates for people with HIV only ignored the onset of AIDS, which is appropriate for risk stratification because the future timing of AIDS would not be known when individuals with HIV only present for assessment. For comparison, we also derived cumulative incidence estimates for individuals with HIV only that treated AIDS as a competing event (Appendix Table A1, online only). As expected,

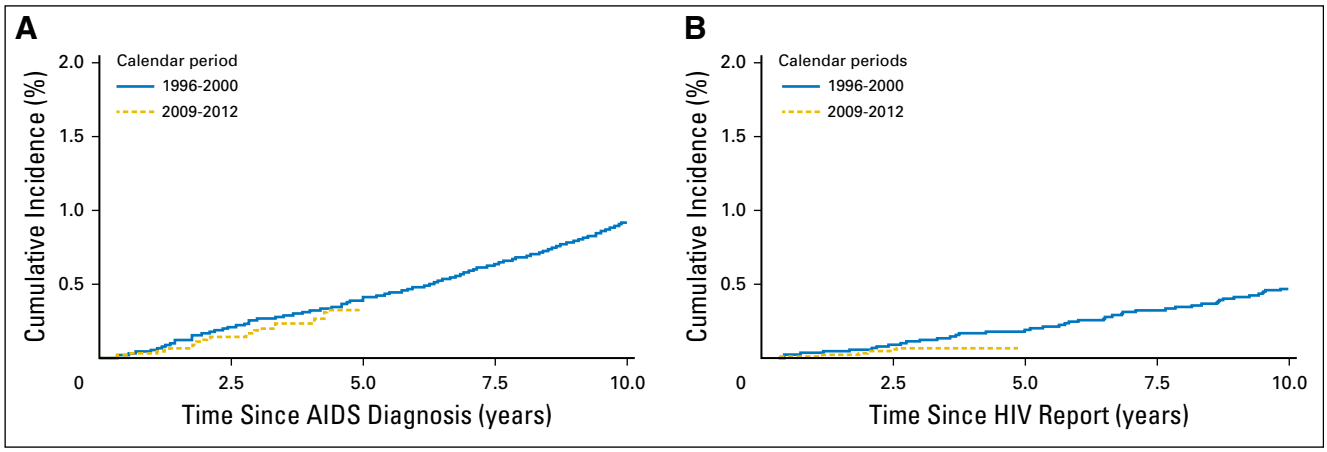

Fig 3. Cumulative incidence of anal cancer in men who have sex with men (MSM) with HIV infection in the United States during 1996 to 2000 and 2009 to 2012. Cumulative incidence of anal cancer among (A) MSM with AIDS and (B) MSM with HIV only as a function of follow-up time. The solid line corresponds to MSM with HIV reported or an AIDS diagnosis during the 1996 to 2000 calendar period, and the dashed line corresponds to HIV reported or an AIDS diagnosis during 2009 to 2012.

these estimates were generally lower than those that ignored AIDS as a competing event because many anal cancers occurred after AIDS onset. Under either scenario, the onset of AIDS can be viewed as a sentinel event that transitions individuals to a higher-risk stratum when they would need heightened consideration for screening. Finally, our long-term estimates of cumulative incidence were largely based on the incidence during 2000 to 2008. Given the possibility of recent declines in anal cancer incidence and cumulative incidence (Figs 1 and 3), an update of these results would be useful.

Strengths of our study include the availability of population-based data on anal cancer in people with HIV infection from eight US states and Puerto Rico over the entire course of the HAART era. The study's size allowed us to assess patterns in incidence despite the rarity of anal cancer, and we measured cumulative incidence to provide perspective about the utility of screening.

A potential limitation is that the included HIV and cancer registries covered various calendar-year intervals, which could have affected the time trends. However, both registries with data accumulated before 1999 and those with data only after 1999 demonstrated a flat or perhaps decreasing trend since 2002. Another limitation is that we lacked individual data on HAART use, HIV disease markers (CD4 count, HIV viral load), and anal HPV infection. Finally, the cumulative incidence is only one factor that needs to be considered in assessing whether screening would be useful. Incorporation of information about the sensitivity and specificity of screening tests as well as the benefits and harms from the work-up and treatment of people with positive test results would be important.

Approaches for anal cancer screening and prevention currently are being evaluated among people with HIV infection.[31] The Anal Cancer HSIL Outcomes Research study is an ongoing phase III multicenter clinical trial in the United States whose primary aim is to determine whether the treatment of anal HSILs is effective at reducing anal cancer incidence in people with HIV.[32] The study has an accrual target of 5,058 men and women age $\geq$ 35 years with HSIL, and a biobank is being created for future studies of the natural history of HSIL progression to anal cancer.

HPV vaccination coverage is still suboptimal in the United States.[33,34] Because vaccination has only been available for one decade and because it takes multiple decades after infection to develop anal cancer, current anal cancer trends have not yet been affected by vaccination. Future studies should evaluate the impact of HPV vaccination coverage on anal cancer trends in the US general population and high-risk subgroups, including people with HIV infection.

In conclusion, this study demonstrates the increased burden of anal cancer among people with HIV, particularly MSM. The results identify some subgroups with the highest cumulative incidence that may most benefit from screening and prevention. The recent apparent decline in incidence is encouraging and may reflect delayed benefits of increasing use of HAART. However, because anal cancer incidence increases with age, the overall burden of patients with this disease may start to increase again with the aging of the US HIV population. Continued monitoring of trends for this malignancy is necessary.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Collection and assembly of data: Eric A. Engels
Data analysis and interpretation: All authors
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Final approval of manuscript: All authors
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Support

Supported in part by the Intramural Research Program of the National Cancer Institute.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Anal Cancer Risk Among People With HIV Infection in the United States

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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No relationship to disclose

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No relationship to disclose

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No relationship to disclose

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No relationship to disclose

Acknowledgment

The authors gratefully acknowledge the support and assistance provided by individuals at the following state HIV/AIDS and cancer registries: Colorado, Connecticut, Georgia, Maryland, Michigan, New Jersey, New York, Puerto Rico, and Texas. We also thank Timothy McNeel at Information Management Services for programming support.

The views expressed in this paper are those of the authors and should not be interpreted to reflect the views or policies of the National Cancer Institute, HIV/AIDS or cancer registries, or their contractors. This research was supported in part by the Intramural Research Program of the National Cancer Institute.

The following cancer registries were supported by the SEER Program of the National Cancer Institute: Connecticut (HHSN261201300019I) and New Jersey (HHSN261201300021I, N01-PC-2013-00021). The following cancer registries were supported by the National Program of Cancer Registries of the Centers for Disease Control and Prevention: Colorado (5U58DP003868-04), Georgia (5U58DP003875-01), Maryland (5NU58DP003919-05-00), Michigan (5U58DP003921-03), New Jersey (NU58/DP003931-05-00), New York (U58/DP003879), and Texas (5U58DP000824-04). The New Jersey State Cancer Registry was also supported by the state of New Jersey, the Maryland Cancer Registry was supported by the State of Maryland and the Maryland Cigarette Restitution Fund, and the New York State Cancer Registry was also supported by the state of New York. The following HIV registries were supported by HIV Incidence and Case Surveillance Branch of the Centers for Disease Control and Prevention, National HIV Surveillance Systems: Colorado, Connecticut (5U62PS001005-05), Michigan (U62PS004011-02), and New Jersey (U62PS004001-2).

Appendix

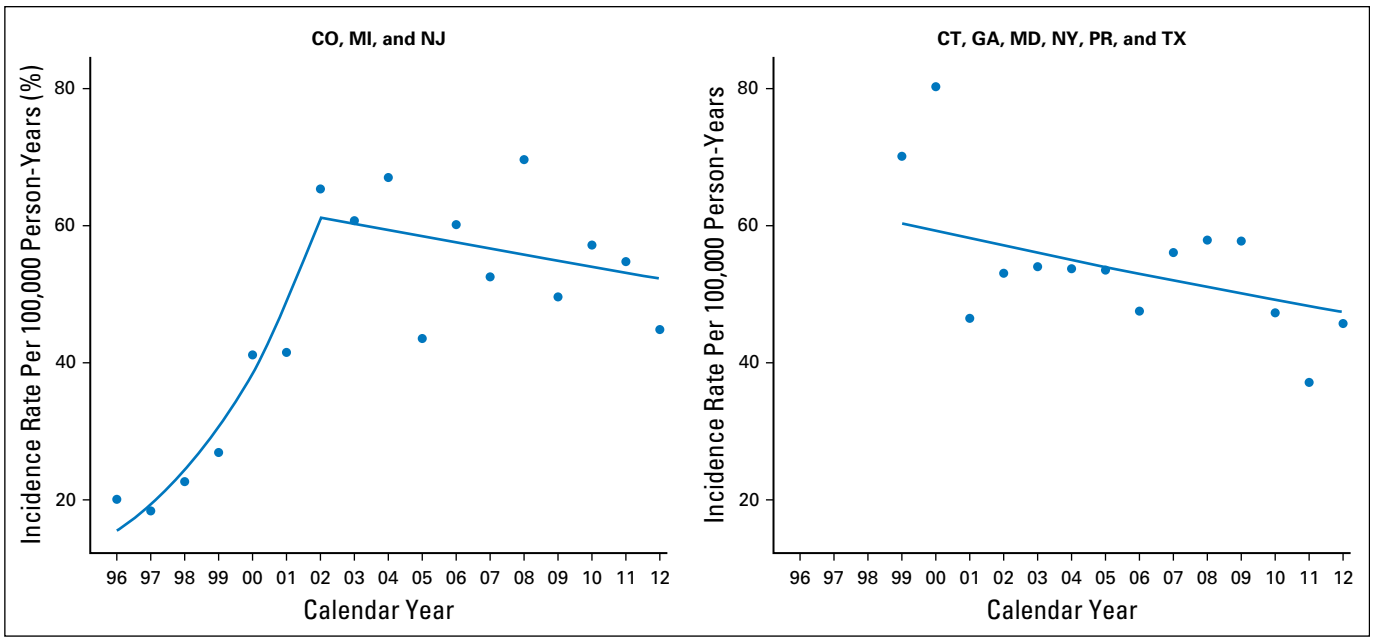

Fig A1. Trend in incidence rate of anal cancer among people with HIV infection, 1996 to 2012. Dots indicate the observed incidence of anal cancer among people with HIV in the study population as a function of calendar year.

Table A1. Cumulative Incidence of Anal Cancer Among People With HIV Only and by Treating AIDS Diagnosis as a Competing Event

Sex/Risk Group Stratified by Age*	Cumulative Incidence, % (95% CI)	
	HIV Only, 5 Years	HIV Only, 10 Years
MSM		
< 30	0.02 (0.00 to 0.04)	0.05 (0.01 to 0.10)
30-44	0.08 (0.05 to 0.12)	0.20 (0.14 to 0.26)
45-59	0.25 (0.16 to 0.35)	0.50 (0.32 to 0.67)
≥ 60	0.26 (0.00 to 0.55)	0.79 (0.11 to 1.48)
Other males		
< 30	0.01 (0.00 to 0.03)	0.01 (0.00 to 0.03)
30-44	0.05 (0.02 to 0.08)	0.08 (0.04 to 0.13)
45-59	0.04 (0.01 to 0.07)	0.09 (0.04 to 0.15)
≥ 60	0.06 (0.00 to 0.18)	0.16 (0.00 to 0.40)
Females		
< 30	0.02 (0.00 to 0.04)	0.04 (0.00 to 0.09)
30-44	0.04 (0.01 to 0.06)	0.07 (0.04 to 0.11)
45-59	0.07 (0.02 to 0.12)	0.11 (0.03 to 0.18)
≥ 60	0.08 (0.00 to 0.24)	0.08 (0.00 to 0.24)

Abbreviation: MSM, men who have sex with men.
*Age is in years measured at HIV report.