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Hazard of Cervical, Oropharyngeal, and Anal Cancers in HIV-infected and HIV-uninfected Medicaid Beneficiaries

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Abstract

Background: HIV+ individuals are disproportionately at risk for HPV-associated cancers, but the magnitude of risk estimates varies widely. We conducted a retrospective study using a large United States-based cohort to describe the relationship between HIV infection and incident cervical, oropharyngeal, and anal cancers.

Methods: Using 2001 – 2012 US Medicaid data from fourteen states, we matched one HIV+ to three HIV- enrollees on sex, race, state, age, and year, and followed persons for up to ten years. We developed Cox proportional hazards models comparing HIV+ to HIV- for time to cancer diagnosis adjusted for demographic and comorbidity attributes.

Results: Our cohorts included 443,592 women for the cervical cancer analysis, and 907,348 and 906,616 persons for the oropharyngeal and anal cancer analyses. The cervical cancer cohort had a mean age of 39 years and was 55% Black. The oropharyngeal and anal cancer cohorts were 50% male, had a mean age of 41 years, and were 51% Black. We estimated the following hazard ratios: cervical cancer, 3.27 (95% CI 2.82 – 3.80); oropharyngeal cancer, 1.90 (95% CI 1.62 – 2.23) (both sexes), 1.69 (95% CI 1.39 – 2.04) (males), and 2.55 (95% CI 1.86 – 3.50) (females); and anal cancer, 18.42 (95% CI 14.65 – 23.16) (both sexes), 20.73 (95% CI 15.60 – 27.56) (males), and 12.88 (95% CI 8.69 – 19.07) (females).

Conclusion: HIV+ persons were at an elevated risk for HPV associated cancers, especially anal cancer.

Impact: Medicaid claims data corroborate previous estimates based on registries and clinical cohorts.

Keywords

HIV/AIDS; cancer; HPV; Medicaid; epidemiology

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INTRODUCTION

Human papillomavirus (HPV) infection is the most prevalent sexually transmitted disease in the US: One in four people are currently infected, and nearly all sexually active people will become infected at some point during their lives (1–3). Although most HPV infections clear spontaneously, persistent infection with oncogenic types can result in carcinoma of the cervix, other anogenital sites, and the head and neck (4, 5). Genotyping assays of histologically-verified archived tissue samples detected HPV DNA in 91% of cervical, 69% of vulvar, 75% of vaginal, 91% of anal, 63% of penile, 70% of oropharyngeal, 32% of oral cavity, and 21% of laryngeal invasive cancers (6). For the period 2012 – 2016, an average of 34,800 HPV-attributable cancers were diagnosed annually in the US; the most affected sites were the cervix (10,900 new cases annually), the oropharyngeal region (13,500 new cases annually), and the anus (6,200 new cases annually, including rectal squamous cell carcinoma (SCC)) (7). The National Cancer Institute and the US Centers for Disease Control and Prevention (CDC) (8) reported average yearly age-adjusted incidence rates for the period 2012 – 2016 for cervical cancer (7.2/100,000 females), oropharyngeal cancer (8.5/100,000 males, and 1.7/100,000 females), and anal/rectal SCC (1.3/100,000 males, and 2.3/100,000 females).

Known or suspected risk factors for the development of HPV-associated cancers include age, sex, and race (9, 10), tobacco use and alcohol abuse (11–21), exogenous hormone use (22, 23), sexual behaviors (24–28), and pregnancy/parity characteristics (24, 29, 30). There is also a strong association between human immunodeficiency virus (HIV) infection and incidence of HPV cancers (31–34), due to molecular and cellular factors which enhance coinfection, allow persistence, and promote carcinogenesis (35–37); however, estimates of the effect of HIV infection on HPV cancer vary widely across studies. In previous US studies, HIV-infected individuals have been largely drawn from clinical cohorts or HIV registries, and are usually compared to the general population; further, models are often adjusted only for demographics, and not for other risk factors. To more precisely estimate the elevated risk for HPV-related cancers in persons with HIV, our analysis was based on HIV-infected (HIV+) and HIV-uninfected (HIV-) patients from the same nationally representative sample of US Medicaid beneficiaries, matched on five demographic variables. Because our analysis used administrative (claims) data, we were also able to control for comorbid conditions, substance use disorder, tobacco use, and use of hormonal medications. For this study, we examined the effect of HIV status on the incidence of the three most prevalent HPV-associated cancers: cervical, oropharyngeal, and anal carcinoma.

MATERIALS AND METHODS

We used a retrospective cohort study design with claims data from the US Medicaid program. Medicaid insures roughly over 40% of the HIV-infected individuals in the US (38), and is the largest single repository of claims data for this population. The fourteen states with the highest HIV prevalence (NY, CA, FL, TX, MD, NJ, PA, IL, GA, NC, VA, LA, OH, and MA) account for 75% of US HIV cases (39). We obtained 100% Medicaid Analytic eXtract (MAX) Personal Summary (PS), Inpatient (IP), Long Term Care (LT), Prescription Drug (Rx), and Other Therapy (OT) files for these states for the years 2001 – 2012.

Sample Selection

We selected all beneficiaries with at least 24 months of continuous enrollment (two month gap allowed) in a Medicaid fee for service (FFS) or comprehensive managed care (MCO) plan, aged between 18 and 64 years at the start of enrollment, and not dually Medicare/Medicaid enrolled. We identified HIV+ persons using an algorithm based on HIV diagnostic codes, antiretroviral therapy (ART) prescription records, diagnostic codes for HIV wasting and HIV dementia, and claims for CD4+ T-cell testing (test results not available), as described elsewhere (40); our algorithm for flagging HIV+ women did not include a diagnosis of cervical cancer. An index date (start of follow-up) was calculated as follows: For HIV+ persons, the index date was the first HIV claim date, or the first date the enrollee had 24 preceding continuous months of Medicaid enrollment, whichever was later. For HIV- persons, the index date was the first date an enrollee had 24 preceding continuous months of enrollment.

For all analyses, we excluded those persons for whom sex data (male vs. female) were missing. For the cervical cancer analysis, we excluded those persons coded as males, and those individuals with one or more claims for a total hysterectomy (cervix removed) with a claim date prior to the index date (ICD-9-CM (41) and CPT-4 (42) hysterectomy codes were reviewed by a local expert, and are listed in Supplementary Table S3). Persons with prevalent cervical, oropharyngeal, or anal cancer on or before the index date were excluded from analysis for that cancer. After applying exclusions, we matched HIV+ and HIV- persons on sex, race, geographic state of enrollment on the index date, age (in years) on the index date, and calendar year of the index date. We randomly matched three HIV- persons to each HIV+ person, a ratio maximizing the number of HIV- matches per HIV+ person and the number of HIV+ persons included in the analysis. See Figure 1.

Outcomes

We followed all persons from the index date until outcome or censor: end of Medicaid enrollment, attainment of age 65, end of study period (December 31, 2012), or, for the cervical cancer analysis, the first claim which included a procedure code for a total hysterectomy, whichever came first. The outcomes were incident cervical, oropharyngeal, or anal cancer during follow-up. An incident diagnosis required one or more IP claims, one or more LT claims, or two or more OT claims separated by at least 30 days, with an applicable diagnostic code in any diagnostic code field. For cervical cancer, we used International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) (41) diagnostic codes 180, 180.0, 180.1, 180.8, and 180.9; for oropharyngeal cancer, 141.0, 141.6, 145.3, 145.4, 146, 146.0, 146.1, 146.2, 146.3, 146.4, 146.5, 146.6, 146.7, 146.8, and 146.9; and for anal cancer, 154.2 and 154.3. See Supplementary Table S4 for diagnostic code definitions.

Covariates

Categories of age at index date (18–24, 25–34, 35–44, 45–54, and 55–64) were assigned for the purpose of cohort description. Covariates considered for the models included age (in years) at index date, sex (male or female), race (White, Black, Hispanic, Asian/Pacific Islander/Native American, or Multiracial/Unknown), index state, index year, binary indicators for five categories of comorbidities and three classes of substance use/abuse at

baseline, number of comorbidity categories at baseline, and a binary indicator for exogenous hormone use during follow-up. At analysis, none of these covariates had any missing data.

We based our indicators for comorbidities on the presence of ICD-9 diagnostic codes for 90 conditions, following the model of the Veterans Aging Cohort Study (VACS) (43). We assigned a positive binary if an applicable code was included in one or more IP claims, one or more LT claims, or two or more OT claims separated by at least 30 days. We aggregated 23 of the 90 conditions into five major categories of disease, as shown in Supplementary Table S5: diabetes, cardiovascular, liver, pulmonary, and psychiatric. We built a crude comorbidity score (0 to 5) by summing the number of major disease categories per person prevalent during baseline.

We created three broad classes of substance use/abuse (alcohol abuse, drug abuse, and tobacco use) from lists of diagnostic and procedure codes developed by the US Department of Health and Human Services' Substance Abuse and Mental Health Services Administration (SAMHSA) (44), VACS, and selected authors (45–49). We assigned a positive binary indicator for each class if a person had one or more IP claims, one or more LT claims, or two or more OT claims separated by at least 30 days containing any code within the class.

We built a binary indicator for possession during follow-up of any medication listed under the Lexicomp® (50) parent class sex hormones; this class includes androgens and anabolic steroids, contraceptives, estrogens, gonadotropin-releasing hormone and analogs, gonadotropins, progestins, and sex hormone combinations.

Statistical analysis

We calculated descriptive statistics for patient characteristics by exposure status, and used the chi-square and t-tests for differences in explanatory variables between HIV status groups. We used the life-table method to compute hazard at the midpoint of each yearly interval of follow-up time (51), and plotted the cumulative hazard over time for each stratum (HIV status and sex).

We used a Cox proportional hazard regression model with a maximum likelihood estimation (52) to estimate the hazard ratios of the outcome by exposure status, and to evaluate the effects of the explanatory variables on the hazard function. We tested the assumption of proportionality by plotting the log log survivor function, $\log [-\log S(t)]$, and by examining the martingale and Schoenfeld residuals. The final models included the following covariates: at the index date, sex (oropharyngeal and anal cancer only), race, state, age (in years), and year; during the baseline period, comorbidity score, and presence of alcohol abuse, drug abuse, and tobacco use; and during follow-up, any sex hormone use. We accounted for intraclass dependence among persons having the same match identification numbers (assigned to each set of four persons, one HIV+ and three HIV-) by following the approach developed by Lee, *et al.* (53) which incorporates the match identification numbers into the regression.

To explore the validity of including claims for MCO enrollees, as a sensitivity analysis we compared the results from this combined MCO/FFS analysis with those from a prior analysis of cervical and oropharyngeal cancer incidence in FFS enrollees only.

We used SAS ver. 9.4 (SAS Institute, Cary, North Carolina, USA) for all analyses. The Brown University Institutional Review Board approved this project with a waiver of informed consent.

RESULTS

Our study included 110,898 HIV+ and 332,694 matched HIV- females for the cervical cancer analysis; 226,837 HIV+ and 680,511 matched HIV- persons for the oropharyngeal cancer analysis; and 226,654 HIV+ and 679,962 matched HIV- persons for the anal cancer analysis. The cervical cancer matched cohort had a mean age of 39 years, and was 55% Black and 19% Hispanic/Latina. The oropharyngeal and anal cancers matched cohorts both had a mean age of 41 years, and were both 50% male, 51% Black, and 20% Hispanic/Latino (Table 1). During follow-up (mean 3.32 – 3.40 years, SD 3.18 – 3.23 years), there were 828 cases of cervical cancer, 713 cases of oropharyngeal cancer (534 males, 179 females), and 649 cases of anal cancer (451 males, 198 females) in the matched cohorts (Table 2). Characteristics and HPV cancer events during follow-up for the unmatched as well as matched cohorts are described in Supplementary Tables S1 and S2.

The plots of cumulative hazards for progression to cervical, oropharyngeal, and anal cancers illustrate that cancer incidence was uniformly higher in HIV+ persons throughout the entirety of the follow-up period (Figure 2). Tests indicated no major violations of the proportional hazards assumption. The adjusted Cox proportional hazards models (Table 3) show a HR of 3.27 (95% CI 2.82 – 3.80) for cervical cancer. For oropharyngeal cancer, the HR for both sexes combined was 1.90 (95% CI 1.62 – 2.23); for males only, the HR was 1.69 (95% CI 1.39 – 2.04), and for females only, 2.55 (95% CI 1.86 – 3.50). For anal cancer, the HR for both sexes combined was 18.42 (95% CI 14.65 – 23.16); for males only, the HR was 20.73 (95% CI 15.60 – 27.56), and for females only, 12.88 (95% CI 8.69 – 19.07).

Our sensitivity analyses yielded findings consistent with our primary analyses. The adjusted HRs for the FFS-only sample were 2.60 (95% CI 2.16 – 3.12) for cervical cancer, 1.75 (95% CI 1.41 – 2.16) for oropharyngeal cancer in both sexes, 1.52 (95% CI 1.17 – 1.96) for oropharyngeal cancer in males, and 2.39 (95% CI 1.61 – 3.54) for oropharyngeal cancer in females.

DISCUSSION

Using a population-based sample of Medicaid beneficiaries, this study corroborates previously published results showing HIV infection is associated with an increased risk of cervical, oropharyngeal, and anal cancers. For females, the hazard ratios for cervical, oropharyngeal, and anal cancers were 3.27 (95% CI 2.82 – 3.80), 2.55 (95% CI 1.86 – 3.50), and 12.88 (95% CI 8.69 – 19.07), respectively. For males, the hazard ratios for oropharyngeal and anal cancers were 1.69 (95% CI 1.39 – 2.04) and 20.73 (95% CI 15.60 – 27.56), respectively.

Published estimates of the effect of HIV infection on HPV cancer differ, as studies vary in data source, years studied, comparator HIV- population, and covariates. Table 4 shows attributes and results of some of the largest, most recent North American studies comparing the risk of invasive HPV-associated cancers in HIV+ and HIV- individuals. Those with the largest samples (Chaturvedi *et al.* (54), Hernandez-Ramirez *et al.* (55), and Engels *et al.* (56)) compared HPV cancer incidence rates for individuals from linked HIV and cancer registries to those of the general population. (Chaturvedi *et al.* and Engels *et al.* limited their analysis of HIV+ individuals to those with an AIDS diagnosis.) Others (Beachler *et al.* (57), Patel *et al.* (58), and Abraham *et al.* (59)) examined somewhat smaller samples of pooled cohorts from, for example, the North American AIDS Cohort Collaboration on Research and Design, and also used the general population as a comparator. Only a few studies compared HPV cancer incidence in HIV+ persons with matched HIV- persons from the same data source: Park *et al.* (60) examined data from the Veterans Aging Cohort Study, and Silverberg *et al.* (61) used data from the Kaiser Permanente California-enrolled population. Our methods resulted in estimates of comparative risk that were somewhat lower than most of these estimates for cervical cancer; comparable to the linked registry studies and VACS and Kaiser Permanente studies, but lower than the pooled cohort studies, for oropharyngeal cancer; and very close to the linked registry studies but considerably lower than the others for anal cancer.

US Medicaid beneficiaries have poorer health than privately insured persons (62), even controlling for income (63), which may explain some of the divergence of our estimates from those previously published. The divergence may also be explained by improved internal validity and precision of our estimates made possible by the size and breadth of the Medicaid enrollment and claims files. The large size of our MAX dataset allowed us to select HIV+ and HIV- comparison groups from the same Medicaid population, minimizing unmeasured confounding due to differences in patient characteristics of the two exposure groups; further, HIV+ and HIV- individuals were matched on five demographic factors, ensuring an even distribution of the matching factors among the exposed and unexposed, no association between the matching factors and the exposure, and minimal confounding of the crude effect estimate by the matching factors. The variety and detail of diagnostic, procedure, and prescription drug data allowed us to exclude those not at risk for cervical cancer because of prior total hysterectomy, and to adjust our models for risk factors including prevalent comorbid conditions, substance use disorder, tobacco use, and use of hormonal medications.

Our analysis showed the effects of sociodemographic variables differed across cancer types. In particular, the following demographic characteristics were highly statistically significant ($P < .0001$) in our models: For oropharyngeal and anal cancer, female sex was protective (HR 0.50, 95% CI 0.42 – 0.59 and HR 0.44, 95% CI 0.37 – 0.53, respectively). Hazard increased with age in all models except for anal cancer in males; however, the effect size was small (HRs barely exceeding 1.00). White race was associated with an increased hazard as compared to Black race for anal cancer in males (HR 1.73, 95% CI 1.38 – 2.16). In contrast to these findings, published national data (5) show a greater risk for anal cancer in women than in men, and a lower incidence of anal cancer in White males as compared to Black males. Further, the literature reports an increased risk of cervical cancer in Black women as

compared to White women, and of oropharyngeal cancer in Whites as compared to Blacks, associations which were not statistically significant in our models. This is likely a result of the demographic, behavioral, and clinical differences in our analytic cohort as compared to the general US population.

Adjustments for substance use disorder and tobacco use, not included in most other studies, resulted in significant associations in our sample. Alcohol abuse had the highest HR of any covariate included in our models (HR 4.8, 95% CI 3.1 – 7.4, for oropharyngeal cancer in females.) The CDC classifies cancers of the oral cavity and pharynx, esophagus, colon and rectum, liver, larynx, and female breast as alcohol-associated cancers, but not cervical or anal cancers (64). Tobacco use was significantly associated with cervical cancer, and with oropharyngeal and anal cancers in males. Our administrative data yielded these results despite a general view that tobacco use indicators in claims data are often incomplete (65). Although tobacco use is widely acknowledged to be a risk factor for cervical cancer (11, 13, 14), the literature is divided on the effects of tobacco on the risk of HPV-associated oropharyngeal cancer (15, 17) and anal cancer (19–21). Abuse of other drugs as reported in our data was significantly associated with a diagnosis of cervical cancer. We also found a reduction in risk of oropharyngeal cancer, and anal cancer in males, associated with other drug abuse; this finding warrants further work to elucidate this relationship.

Prescription drug data allowed for adjustment for hormonal medication use. Our model showed an apparent protective effect of hormone use in the hazard of cervical cancer, a result that contradicts prior reports (11, 12, 22, 23), and of oropharyngeal cancer, consistent with published findings (29). We also saw a protective effect of hormone use for anal cancer in females. By comparison, one study found no significant difference in anal dysplasia rates between HIV+ transgender women exposed to long-term estrogen therapy and HIV+ men who have sex with men (66), and another showed no association between exogenous hormone use and presence of anal squamous intraepithelial lesions (67). Further research into the effect of hormone exposure on HPV-associated cancers is needed.

This analysis has several limitations. First, claims data are intended for payment, not research, and many factors can influence their completeness and accuracy (68–70). We addressed Medicaid enrollment instability by selecting beneficiaries continuously enrolled in FFS or MCO plans for at least two years. We addressed potential omissions of MCO (encounter) claims (71) by comparing results from the combined FFS/MCO sample to those from a FFS-only sample: The HRs for the combined FFS/MCO sample were similar in direction and magnitude to, although somewhat higher than, those for the FFS-only sample, perhaps because of the longer follow-up times. Second, claims data do not include information on certain important risk factors for HPV cancers, such as pregnancy/parity characteristics, sexual history, and undisclosed or unrecorded substance use, nor do they include data on cancer staging or histology. Despite the potential limitations of using claims data, when comparing disease incidence in two subpopulations, results using administrative data may be comparable to those from chart review or clinical registries (16, 72). Third, our findings may not be generalizable to non-Medicaid populations or to the states not covered in our sample.

Our results using Medicaid claims support premises generated from analyses of clinical and histological data sources, particularly large-sample linked registry studies. The MAX datasets are rich in demographic, diagnostic, and health services data that can be used to control for differences in the exposure groups and known or suspected risk factors, all contributing to an increase in precision of the effect estimates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Selection criteria to generate final study cohorts

Figure 2.
Cumulative hazard of cervical, oropharyngeal, and anal cancers, by HIV status and sex

Table 1.

Descriptive and clinical characteristics of the HPV-associated cancer matched cohorts, by exposure status

	Cervical cancer				Oropharyngeal cancer				Anal cancer		
	Overall	HIV+	HIV-		Overall	HIV+	HIV-		Overall	HIV+	HIV-
Total population, n (%)	443,592 (100)	110,898 (25)	332,694 (75)		907,348 (100)	226,837 (25)	680,511 (75)		906,616 (100)	226,654 (25)	679,962 (75)
<i>Characteristics at baseline</i>											
Mean age (SD)	38.51 (11.05)	38.51 (11.05)	38.51 (11.05)		41.07 (10.85)	41.07 (10.85)	41.07 (10.86)		41.07 (10.86)	41.07 (10.85)	41.07 (10.86)
Age group (%)											
18–24	15.06	15.06	15.06		10.22	10.22	10.22		10.23	10.23	10.23
25–34	23.53	23.53	23.53		18.59	18.59	18.59		18.59	18.59	18.59
35–44	31.52	31.52	31.52		32.69	32.69	32.69		32.67	32.67	32.67
45–54	22.45	22.45	22.45		28.36	28.36	28.36		28.36	28.36	28.36
55–64	7.43	7.43	7.43		10.14	10.14	10.14		10.15	10.15	10.15
Sex (% male)	0	0	0		50.18	50.18	50.18		50.15	50.15	50.15
Race/ethnicity (%)											
White	16.91	16.91	16.91		18.87	18.87	18.87		18.85	18.85	18.85
Black	54.95	54.95	54.95		50.95	50.95	50.95		50.96	50.96	50.96
Hispanic/Latino	19.48	19.48	19.48		20.26	20.26	20.26		20.26	20.26	20.26
Asian/PI/NA	4.06	4.06	4.06		4.57	4.57	4.57		4.57	4.57	4.57
Multiracial/Unknown	4.61	4.61	4.61		5.35	5.35	5.35		5.36	5.36	5.36
Index state (%)											
CA	11.50	11.50	11.50		13.17	13.17	13.17		13.16	13.16	13.16
FL	12.16	12.16	12.16		10.22	10.22	10.22		10.23	10.23	10.23
GA	3.60	3.60	3.60		3.13	3.13	3.13		3.13	3.13	3.13
IL	5.93	5.93	5.93		5.46	5.46	5.46		5.46	5.46	5.46
LA	2.92	2.92	2.92		2.36	2.36	2.36		2.36	2.36	2.36
MA	3.58	3.58	3.58		3.93	3.93	3.93		3.93	3.93	3.93
MD	4.36	4.36	4.36		4.25	4.25	4.25		4.25	4.25	4.25
NC	3.33	3.33	3.33		2.88	2.88	2.88		2.88	2.88	2.88
NJ	5.30	5.30	5.30		4.22	4.22	4.22		4.22	4.22	4.22
NY	36.79	36.79	36.79		39.76	39.76	39.76		39.78	39.78	39.78
OH	1.77	1.77	1.77		1.95	1.95	1.95		1.95	1.95	1.95
PA	2.89	2.89	2.89		2.99	2.99	2.99		2.99	2.99	2.99
TX	4.26	4.26	4.26		4.37	4.37	4.37		4.37	4.37	4.37
VA	1.61	1.61	1.61		1.30	1.30	1.30		1.29	1.29	1.29
Index year (%)											
2002	29.85	29.85	29.85		28.41	28.41	28.41		28.41	28.41	28.41

	Cervical cancer				Oropharyngeal cancer				Anal cancer		
	Overall	HIV+	HIV-		Overall	HIV+	HIV-		Overall	HIV+	HIV-
2003	8.67	8.67	8.67		8.44	8.44	8.44		8.44	8.44	8.44
2004	8.25	8.25	8.25		8.27	8.27	8.27		8.27	8.27	8.27
2005	7.31	7.31	7.31		7.48	7.48	7.48		7.48	7.48	7.48
2006	7.07	7.07	7.07		7.24	7.24	7.24		7.24	7.24	7.24
2007	6.09	6.09	6.09		6.41	6.41	6.41		6.40	6.40	6.40
2008	6.09	6.09	6.09		6.28	6.28	6.28		6.28	6.28	6.28
2009	6.43	6.43	6.43		6.53	6.53	6.53		6.53	6.53	6.53
2010	6.71	6.71	6.71		6.95	6.95	6.95		6.95	6.95	6.95
2011	6.51	6.51	6.51		6.80	6.80	6.80		6.79	6.79	6.79
2012	7.03	7.03	7.03		7.20	7.20	7.20		7.20	7.20	7.20
Comorbidities (%)											
Diabetes ^a	9.76	11.30	9.25		11.21	11.42	11.14		11.19	11.43	11.11
Cardiovascular	7.40	10.66	6.31		9.73	11.95	9.00		9.75	11.95	9.01
Liver	5.91	17.53	2.04		8.59	22.96	3.79		8.58	22.97	3.79
Pulmonary	17.18	29.21	13.20		15.98	25.50	12.81		15.98	25.51	12.80
Psychiatric	21.30	35.46	16.58		22.12	34.78	17.90		22.18	34.78	17.98
Mean comorbid score (SD)	0.62 (0.92)	1.04 (1.12)	0.47 (0.80)		0.68 (0.95)	1.06 (1.11)	0.55 (0.85)		0.68 (0.95)	1.07 (1.11)	0.55 (0.85)
Alcohol abuse (%)	8.99	19.17	5.60		13.21	22.98	9.95		13.21	23.00	9.95
Drug abuse (%)	13.18	29.85	7.63		17.16	33.51	11.71		17.21	33.53	11.77
Tobacco use (%)	6.70	12.49	4.77		8.50	14.11	6.63		8.49	14.10	6.63
<i>Characteristics during follow-up</i>											
Hormone use (%)	23.97	30.00	21.96		14.94	23.51	12.08		14.96	23.48	12.11

All p-values from chi-square and t-tests were <.0001, except as noted below.

^aFor Oropharyngeal Cancer, $P=0.0002$

Table 2.

Cervical, oropharyngeal, and anal cancer events for the matched cohorts during follow-up

	Cervical cancer		
	Overall	HIV+	HIV-
Total population, n (%)	443,592 (100)	110,898 (25)	332,694 (75)
Cervical cancer events, n (%)	828 (0.19)	490 (0.44)	338 (0.10)
Follow-up years, total	1,473,685.67	418,128.45	1,055,557.22
Follow-up years, mean (median, SD)	3.32 (2.09, 3.18)	3.77 (2.69, 3.26)	3.17 (1.92, 3.14)
Crude incidence rate per 1000 py	0.56	1.17	0.32
IRR ^a	3.66		
	Oropharyngeal cancer, males		
	Overall	HIV+	HIV-
Total population, n (%)	455,348 (100)	113,837 (25)	341,511 (75)
Oropharyngeal cancer events, n (%)	534 (0.12)	183 (0.16)	351 (0.10)
Follow-up years, total	1,523,009.27	398,756.15	1,124,253.11
Follow-up years, mean (median, SD)	3.34 (2.09, 3.20)	3.50 (2.34, 3.21)	3.29 (2.00, 3.20)
Crude incidence rate per 1000 py	0.35	0.46	0.31
IRR ^a	1.47		
	Oropharyngeal cancer, females		
	Overall	HIV+	HIV-
Total population, n (%)	452,000 (100)	113,000 (25)	339,000 (75)
Oropharyngeal cancer events, n (%)	179 (0.04)	91 (0.08)	88 (0.03)
Follow-up years, total	1,534,128.77	436,330.12	1,097,798.64
Follow-up years, mean (median, SD)	3.39 (2.17, 3.23)	3.86 (2.77, 3.31)	3.24 (2.00, 3.19)
Crude incidence rate per 1000 py	0.12	0.21	0.08
IRR ^a	2.60		
	Anal cancer, males		
	Overall	HIV+	HIV-
Total population, n (%)	454,692 (100)	113,673 (25)	341,019 (75)
Anal cancer events, n (%)	451 (0.10)	393 (0.35)	58 (0.02)
Follow-up years, total	1,523,523.39	397,602.51	1,125,920.88
Follow-up years, mean (median, SD)	3.35 (2.09, 3.21)	3.50 (2.34, 3.21)	3.30 (2.00, 3.21)
Crude incidence rate per 1000 py	0.30	0.99	0.05
IRR ^a	19.19		

	Cervical cancer		
	Overall	HIV+	HIV-
	Anal cancer, females		
	Overall	HIV+	HIV-
Total population, n (%)	451,924 (100)	112,981 (25)	338,943 (75)
Anal cancer events, n (%)	198 (0.04)	166 (0.15)	32 (0.01)
Follow-up years, total	1,535,258.43	436,019.45	1,099,238.98
Follow-up years, mean (median, SD)	3.40 (2.17, 3.23)	3.86 (2.77, 3.30)	3.24 (2.00, 3.19)
Crude incidence rate per 1000 py	0.13	0.38	0.03
IRR ^a	13.08		

^a Crude Incidence Rate Ratios (HIV+/HIV-) (IRRs) calculated before rounding

Table 3.

Proportional hazards regression models for cervical, oropharyngeal, and anal cancers, by HIV status and sex

	Cervical cancer		Oropharyngeal cancer, males		Oropharyngeal cancer, females		Anal cancer, males		Anal cancer, females
	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)
<i>Unadjusted</i>									
HIV+ vs. HIV-	3.67 (3.19, 4.21)		1.47 (1.23, 1.75)		2.55 (1.90, 3.42)		19.18 (14.56, 25.27)		12.81 (8.77, 18.70)
<i>Adjusted^a</i>									
HIV+ vs. HIV-	3.27 (2.82, 3.80)		1.69 (1.39, 2.04)		2.55 (1.86, 3.50)		20.73 (15.6, 27.56)		12.88 (8.69, 19.07)
Index age (years)	1.02 (1.01, 1.03)		1.11 (1.10, 1.13)		1.10 (1.08, 1.12)		1.01 (1.00, 1.02)		1.04 (1.02, 1.06)
Race, ref=Black									
Asian/PI/NA	0.37 (0.17, 0.78)		0.26 (0.09, 0.69)		0.53 (0.13, 2.19)		0.59 (0.30, 1.16)		0.22 (0.03, 1.62)
Hispanic	0.84 (0.69, 1.03)		0.80 (0.61, 1.05)		0.58 (0.36, 0.95)		0.84 (0.63, 1.13)		0.73 (0.48, 1.12)
Multiracial/Unknown	1.12 (0.83, 1.51)		1.05 (0.74, 1.49)		1.11 (0.62, 1.99)		0.87 (0.56, 1.36)		0.97 (0.49, 1.92)
White	0.99 (0.81, 1.21)		1.20 (0.96, 1.49)		1.00 (0.66, 1.54)		1.73 (1.38, 2.16)		1.69 (1.19, 2.40)
Index year	0.92 (0.90, 0.95)		0.93 (0.90, 0.97)		0.92 (0.85, 0.98)		0.92 (0.88, 0.96)		0.89 (0.82, 0.95)
Comorbid score at baseline	1.05 (0.98, 1.13)		0.88 (0.80, 0.96)		0.85 (0.73, 0.99)		0.89 (0.80, 0.98)		1.01 (0.88, 1.15)
Alcohol abuse at baseline	1.01 (0.82, 1.25)		2.92 (2.34, 3.64)		4.81 (3.14, 7.37)		0.98 (0.73, 1.30)		0.88 (0.58, 1.32)
Drug abuse at baseline	1.70 (1.40, 2.06)		0.59 (0.46, 0.76)		0.66 (0.42, 1.04)		0.71 (0.55, 0.92)		1.36 (0.94, 1.96)
Tobacco use at baseline	1.26 (1.00, 1.57)		1.47 (1.13, 1.90)		1.48 (0.94, 2.33)		1.38 (1.01, 1.89)		1.46 (0.94, 2.25)
Hormone use during follow-up	0.63 (0.53, 0.73)		0.69 (0.50, 0.93)		0.68 (0.48, 0.96)		1.14 (0.92, 1.41)		0.72 (0.53, 0.97)

Bolded results are significant ($P < .05$)^aModel adjusts for variables in the table and for index state

Table 4.

Comparison of largest/most recent North American studies comparing risk of three HPV-associated cancers in HIV-infected and HIV-uninfected persons

Reference	Data source	Years	n, HIV+	Comparator	Adjustors used to compare HIV+ with HIV-	Effect measure	Cervical cancer: estimate (95% CI)	Oropharyngeal cancer: estimate (95% CI)	Anal cancer: estimate (95% CI)
Michaud <i>et al.</i> (2020)	Medicaid claims	2001–2012	~229,000	Medicaid claims	sex, age, race, year, state, SUD, comorbidities, sex hormone use	HR	3.27 (2.82 – 3.80)	1.9 (1.62 – 2.23)	18.42 (14.65 – 23.16)
Chaturvedi <i>et al.</i> (54) (2009)	linked registries	1980–2004	499,230 ^a	general population	sex, age, race, year, registry	SIR	5.6 (4.8 – 6.5)	1.6 (1.2 – 2.1)	
Hernandez <i>et al.</i> (55) (2017)	linked registries	1996–2012	448,258	general population	sex, age, race, year, registry	SIR	3.24 (2.94 – 3.56)	1.64 (1.46 – 1.84)	19.06 (18.13 – 20.03)
Engels <i>et al.</i> (56) (2006)	linked registries	1980–2002	375,933 ^a	general population	sex, age, race, year, registry	SIR	5.3 (3.6 – 7.6) ^b	2.1 (1.4 – 3.0) ^b (all oral cavity/pharynx)	19.6 (14.2 – 26.4) ^b
Beachler <i>et al.</i> (57) (2014)	cohorts	1996–2009	82,375	general population	sex, age, race, calendar period	SIR		3.2 (2.5 – 4.1)	
Patel <i>et al.</i> (58) (2008)	cohorts	1992–2003	54,780	general population	sex, age, race	SRR	10.1 (6.5 – 15.7) ^c	3 (2.0 – 4.5) ^c	59.4 (44.0 – 80.3) ^c
Abraham <i>et al.</i> (59) (2013)	cohorts	1996–2010	13,690	general population	age	SIR	4.1 (2.3 – 6.6)		
Park <i>et al.</i> (60) (2016)	Veterans Aging Cohort Study	1997–2012	44,787	Veterans Aging Cohort Study	sex, age, race, calendar period	IRR		1.7 (1.0 – 2.9) ^d	77 (28 – 218) ^d
Silverberg <i>et al.</i> (61) (2011)	Kaiser Permanente California	1996–2008	20,775	Kaiser Permanente California	sex, age, race, calendar period, region, SUD, overweight/obesity	RR		1.4 (0.9 – 2.1) (all oral cavity/pharynx)	55.7 (33.2 – 93.4)

All estimates are for both sexes combined

^a AIDS only

^b 1996 – 2002 only

^c 2000 – 2003 only

^d 2009 – 2012 only

SUD = substance use disorder (alcohol abuse, drug abuse, tobacco use); HR = hazard ratio; SIR = standardized incidence ratio; SRR = standardized rate ratio; IRR = incidence rate ratio; RR = rate ratio