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Risk of nonkeratinocyte skin cancers in people living with HIV during the era of antiretroviral therapy

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Abstract

Antiretroviral therapy (ART) may alter susceptibility to nonkeratinocyte skin cancers (NKSCs) by improving immunity in people living with HIV (PLWH). Using linked data from HIV and cancer registries in 12 US states/regions during the ART era (1996–2018), we calculated standardized incidence ratios (SIRs) for 27 NKSCs comparing incidence to the general population. Risk factors for NKSCs were evaluated using Poisson regression. There were 2,743 NKSCs diagnosed in 585,706 PLWH followed for 4,575,794 person-years. Kaposi sarcoma (KS) was the most common cancer (82%) followed by melanoma (12%) and cutaneous lymphoma (2.6%). Incidence was elevated for virus-related NKSCs: KS (SIR 147, 95%CI 141–153), diffuse large B-cell lymphoma (DLBCL, 5.19, 3.13–8.11), and Merkel cell carcinoma (MCC, 3.15, 1.93–4.87); elevated incidence for DLBCL and MCC was observed only among PLWH with a prior AIDS diagnosis. KS risk was highest among men who have sex with men. Incidence was not increased for melanoma, adnexal carcinomas, and sarcomas. Melanoma and MCC arose disproportionately on sun-exposed skin, supporting a role for ultraviolet radiation in their development. In conclusion, risk for most NKSCs was similar to the general population during the ART era, suggesting that PLWH without NKSC risk factors may not require intensive skin surveillance.

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AUTHOR CONTRIBUTIONS STATEMENT (CRediT-Compliant)

Conceptualization: EAE, MRS; Methodology: EAE, MRS; Data Curation: YL, EAE, MRS; Formal Analysis: YL, EAE, MRS; Investigation: YL, EAE, MRS; Resources: MS, EAE; Software: YL, EAE, MRS; Writing – Original Draft Preparation: YL, EAE, MRS; Writing – Reviewing and Editing: YL, QL, MH, MS, EAE, MRS; Visualization: YL, MRS; Supervision: EAE, MRS; Project Administration: YL, EAE, MRS

CONFLICT OF INTEREST

The authors state no conflict of interest.

INTRODUCTION

Long-term immunosuppression increases risk for multiple skin cancer types. Individuals with human immunodeficiency virus (HIV) infection and solid organ transplant recipients, who receive immunosuppressive medications to prevent rejection of their transplanted organ, exhibit an increased risk for keratinocyte carcinomas (squamous cell carcinoma and basal cell carcinoma) and a range of nonkeratinocyte skin cancers (NKSCs) (Burgi et al. 2005; Engels et al. 2002; Grulich et al. 2007; Lanoy et al. 2009; O'Reilly Zwald and Brown 2011; Sargen et al. 2022; Silverberg et al. 2013).

Skin cancers have diverse etiologies related to environmental exposures. For example, ultraviolet radiation (UVR) induces DNA damage, which increases risk for keratinocyte carcinomas, melanoma, Merkel cell carcinoma (MCC), and sebaceous carcinoma (Sargen et al. 2020; Watson et al. 2016; Wong et al. 2015). Oncogenic viruses also contribute to the development of some skin cancers. Specifically, Merkel cell polyomavirus (MCPyV) is causally implicated in some MCC cases, and Kaposi sarcoma-associated herpesvirus (KSHV) causes Kaposi sarcoma (KS) (Chang et al. 1994; Feng et al. 2008).

For people living with HIV (PLWH), the deleterious effects of UVR may be augmented by photosensitizing medications, including trimethoprim-sulfamethoxazole, used for pneumocystis pneumonia prevention in those with CD4 counts below 200 cells/μL (Masters et al. 2003). Reduced immune control of oncogenic viruses also increases risk for virus-related cancers such as KS, for which risk is elevated 500-fold for PLWH compared with the general population (Hernández-Ramírez et al. 2017). Some studies also suggest that PLWH have an increased risk for melanoma, while other studies show no difference compared with the general population (Grulich et al. 2007; Lanoy et al. 2009).

ART reverses immunosuppression by reducing viral replication (HIV-CAUSAL Collaboration et al. 2010), and improved immune function could affect skin cancer susceptibility (Asgari et al. 2017). While access to effective ART has increased substantially since 1996, risk for many common and rare skin cancers, including adnexal cancers, cutaneous sarcomas, and primary cutaneous lymphomas, has not been systematically evaluated in PLWH during the current treatment era (Fauci et al. 2019; Sullivan et al. 2021).

In our study, we assessed risk for 27 unique NKSCs in PLWH during the ART era (1996–2018) using population data from the HIV/AIDS Cancer Match (HACM) Study. The potential oncogenic role of UVR was evaluated for the most common skin cancers by assessing whether they occurred more frequently on chronically sun-exposed skin than would be expected based on body surface area. We also evaluated associations between cancer incidence and potential risk factors including measures of immunosuppression. The primary aim of this study was to characterize the spectrum of disease and modifiers of NKSC risk in PLWH, which can provide insights into the etiology of malignant skin tumors and inform skin cancer screening strategies during the ART era.

RESULTS

Skin cancer risk was evaluated for 585,706 PLWH from January 1, 1996, to December 31, 2018, including 359,823 (61.4%) who had an AIDS diagnosis before study entry or during follow-up (Table 1). The median age at HIV diagnosis was 35 years and most cases occurred in men (72.8%). Non-Hispanic Black individuals (51.9%) comprised the largest race/ethnicity group in our cohort, followed by Hispanic (24.2%) and non-Hispanic White (23.9%) individuals. The most common risk group for HIV infection was MSM (41.0%) followed by PWID (17.2%).

A total of 2,743 NKSCs were diagnosed in PLWH during 4,575,794 person-years of follow-up (median follow-up 7.5 years, interquartile range [IQR] 3.6–11.5 years). Overall, 0.5% of PLWH developed a NKSC during the follow-up period. The most common skin cancer was KS (82% of cases; diagnosed in 0.4% of PLWH) followed by melanoma (12%) and cutaneous lymphoma (2.6%). The highest elevation in risk was observed for KS (SIR 147, 95%CI 141–153, Table 2). Risk for non-KS malignancies combined was similar to that of the general population (SIR 0.98, 95%CI 0.90–1.07, for all NKSCs excluding KS). After KS, risk was most elevated for diffuse large B-cell lymphoma (DLBCL, SIR 5.19, 95%CI 3.13–8.11) and MCC (3.15, 1.93–4.87). Risk of melanoma was decreased in PLWH (SIR 0.88, 95%CI 0.79–0.97), but this was not statistically significant after Bonferroni correction. There also appeared to be an elevated risk for lymphangiosarcoma (SIR 163, 95%CI 4.12–906), but this association was based on a single case and was not significant after adjusting for multiple comparisons. The overall risk for adnexal cancers and non-KS sarcomas was not significantly elevated in PLWH.

Incidence for several cancers was increased after a diagnosis of AIDS, including KS (SIR 177, 95%CI 169–185), DLBCL (7.12, 4.15–11.4), and MCC (3.51, 1.96–5.79) (Table 2). Risk of adnexal cancers also appeared to be increased in people with a prior AIDS diagnosis (SIR 2.01, 95%CI 1.12–3.31), but this association was not significant after Bonferroni correction. Overall risk for non-KS malignancies was similar to the general population (SIR 1.00, 95%CI 0.90–1.12, for all NKSCs excluding KS) for people with a prior AIDS diagnosis. Furthermore, among individuals with HIV only (no prior AIDS diagnosis), risk was not elevated for MCC or DLBCL.

Multivariate models evaluating potential risk factors are reported for KS (Table 3), melanoma (Table 4), MCC (Table 4), and lymphoma (Table 4). Univariate models are presented in the data supplement (Supplementary Tables S2 and S3).

KS risk was highest in MSM (IRR 9.84, compared with females who had other/unknown risk factors for HIV, Table 3). Males, individuals with a prior AIDS diagnosis, and non-White PLWH (i.e., non-Hispanic Black and Hispanic) also had an elevated risk for KS ($P<0.05$ for all comparisons). In contrast, risk for KS was lowest in people greater than 15 years removed from their HIV diagnosis (IRR 0.45, compared with ≤ 5 years from diagnosis) and those aged 60 years or older (IRR 0.33, compared with those aged 0–39 years).

As shown in Table 4, male sex was not a risk factor for melanoma, MCC, or lymphoma. MSM and PWID also did not exhibit an increased risk for these cancers. Additionally, having a prior AIDS diagnosis was not a risk factor for melanoma or MCC, although it was associated with a borderline increased risk for lymphoma (IRR 1.70, P=0.05). Increased age was a risk factor for melanoma, MCC, and lymphoma (P_{trend}<0.05), with individuals aged 60 years and older exhibiting the highest risk for these cancers. Melanoma incidence decreased over time following an HIV diagnosis (P_{trend}=0.001, Table 4). Additionally, progressively later calendar periods were associated with a decreased risk for lymphoma (P_{trend}=0.001), although this trend was not seen for melanoma or MCC.

For PLWH, risk of melanoma and MCC was lower in non-Hispanic Black individuals, and melanoma risk was similarly decreased for Hispanic individuals (P<0.05 for all analyses, vs. non-Hispanic White). In contrast, lymphoma risk did not differ according to race/ethnicity.

Body mapping analyses (Figure 1) demonstrated that multiple cancer types occurred disproportionately on the sun-exposed head and neck region relative to body surface area, especially adnexal cancers (O:E for head and neck, 6.43), DLBCL (4.44), and MCC (3.92). Other cancers occurring with higher-than-expected frequencies on the head and neck region included lymphomas (O:E 3.33) and melanoma (O:E 1.67). In contrast, KS was over-represented on both the head and neck (O:E 1.25) and lower extremity (1.54).

DISCUSSION

This study is the largest population-based analysis to systematically evaluate risk for common and rare NKSCs in PLWH during the ART era (1996–2018). We demonstrate that KS risk remains elevated in PLWH, but incidence for most other NKSCs is not increased compared to the general population. As we review below, our results suggest that oncogenic viruses, severity of immunosuppression, and UVR contribute to skin carcinogenesis in PLWH, highlighting the etiologic heterogeneity of malignant skin tumors in this population.

The highly elevated risk of KS that we observed is caused by multiple factors including the high prevalence of KSHV infection in PLWH, immunosuppression, and potentially direct tumor-promoting effects of HIV (Engels et al. 2011; Ensoli et al. 1994; Ensoli et al. 1990; Sargen et al. 2022). MSM exhibited the greatest risk for KS, which likely reflects frequent sexual transmission rates of KSHV in this subgroup (Butler et al. 2009; Martin et al. 1998; Zhang et al. 2022). KS risk also declined significantly with longer time since HIV diagnosis and across calendar periods, probably reflecting trends in the uptake of ART (Forsythe et al. 2019).

Incidence for virus-related cancers appeared to correlate with immunosuppression severity. For example, risk for MCC (associated with MCPyV) and DLBCL (associated with Epstein-Barr virus [EBV] in PLWH) (Chapman et al. 2021) was elevated in people with a prior AIDS diagnosis, but not in those with HIV only (without a prior AIDS diagnosis). Declining CD4 counts have been associated with an increased risk for EBV-related systemic DLBCL (Biggar et al. 2007; Chapman et al. 2021), and poorly-controlled HIV infection is also associated with higher loads of cutaneous MCPyV-DNA (Wieland et al. 2011), suggesting

that severe immune suppression allows for persistence of these viruses, increasing the likelihood of these infectious agents causing malignant transformation of host cells. A viral etiology has been suggested for sebaceous carcinoma because of its highly increased incidence in solid organ transplant recipients (Sargen et al. 2022; Sargen et al. 2021; Sargen et al. 2020). A prior analysis of people with AIDS in the HACM Study (with data from 1980–2004) found an elevated risk of sebaceous carcinoma (Lanoy et al. 2009), but a similar elevation was not observed in the present study with more recent calendar years during the ART era. We also did not observe an elevated risk for non-KS sarcomas in PLWH, except for a highly elevated risk for lymphangiosarcoma, although this association was based on a single case.

Chronic UVR exposure also appears to contribute to the development of several malignant skin tumors in PLWH. Non-Hispanic Black and Hispanic PLWH, who tend to have increased photoprotective melanin pigment in their skin, exhibited a lower risk for melanoma and MCC than non-Hispanic White individuals. Similarly, our body mapping analyses demonstrated that melanoma, MCC, and adnexal cancers occurred disproportionately on sun-exposed skin of the head and neck. We observed similar patterns for KS and cutaneous lymphomas, suggesting that UVR-induced immunosuppression in the skin could be playing a role (Cahoon et al. 2018; Cahoon et al. 2017; Sargen et al. 2022). The high prevalence of KS on the lower extremity skin, including the feet where there is poor oxygenation, may reflect the proposed role of hypoxia in KS development (Davis et al. 2001).

Studies including data from the pre-ART era (pre-1996) demonstrated an increased risk for melanoma in PLWH (Grulich et al. 2007). In our cohort, there appeared to be a decreased risk of melanoma in PLWH compared with the general population, although this association was nonsignificant. The borderline decreased risk for melanoma and the decline with longer time since HIV diagnosis could be attributable to increased skin surveillance in PLWH over time (Goedert et al. 2016; Johnson et al. 2017; Silverberg et al. 2013), resulting in the detection and removal of premalignant dysplastic nevi and *in-situ* melanomas. Neither severity of immunosuppression (prior AIDS diagnosis) nor its duration (time since HIV diagnosis) was associated with melanoma risk in multivariate models.

Skin cancer screening recommendations have not yet been incorporated into HIV cancer surveillance guidelines by the Infectious Disease Society of America (Thompson et al. 2021; Yeung et al. 2019). However, skin exams have been advocated by some authors due to the elevated risk of certain skin cancers, notably KS, in PLWH (Goedert et al. 2016; Johnson et al. 2017; Silverberg et al. 2013). While KS risk remains highly elevated, absolute risk for this cancer type is relatively low (0.4% of PLWH in our study developed KS during the follow-up period). Additionally, it has not been demonstrated that early detection of KS by periodic screening would result in decreased morbidity and mortality from this cancer type.

Major strengths of the current study include its representativeness of PLWH in the US, geographic diversity of HIV registries, and duration of follow-up. For some cancers, the number of cases was limited, which prevented us from evaluating risk factors. We also did not have information on CD4 counts and viral load during the follow-up period

to measure the severity of immunosuppression. Instead, we used prior AIDS diagnosis and time since HIV diagnosis as indirect measures of immunosuppression severity and duration, respectively. We restricted our analysis to the ART era, but individual data on ART medications and adherence to therapy, which could also impact skin cancer risk, were not available. Lastly, multiple comparisons could lead to false positive associations. We addressed this issue by performing a Bonferroni correction for our SIR estimates. We also report P-values for our IRR estimates to indicate the strength of the statistical evidence.

In conclusion, our results support that immunosuppression, oncogenic viruses, and chronic UVR exposure contribute to the development of specific skin cancer types in PLWH. During the ART era, risk for KS remains highly elevated. Elevations in risk for other virus-related cancers (DLBCL and MCC) were observed only for people with a prior AIDS diagnosis. For most NKSCs, risk was not elevated compared to the general population, suggesting that PLWH may not require intensive skin surveillance in the absence of other risk factors.

MATERIALS & METHODS

The HACM Study links public health surveillance information for 10 US states, the District of Columbia, and Puerto Rico on HIV and cancer diagnoses, both of which are notifiable conditions to health departments. Therefore, 100% of HIV and cancer diagnoses are captured, except that keratinocyte cancers (squamous cell carcinoma, basal cell carcinoma) are not reported to cancer registries. In addition, some cancer diagnoses in PLWH could be missed in the HACM Study due to incomplete sensitivity of the registry linkage or migration of PLWH out of the cancer registry catchment areas. The HACM Study was approved by institutional review boards at participating HIV and cancer registries (when required). Further information is available online (https://hivmatch.cancer.gov/) and described in prior publications (Hernández-Ramírez et al. 2017; Mahale et al. 2020). This article follows Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

PLWH were followed from their HIV report date or beginning of registry coverage (whichever was later) to the occurrence of one of the following events: death, age 85, or end of registry coverage. Cancer diagnoses were identified using International Classification of Diseases for Oncology (third edition) histology codes (Supplementary Table S1). Site codes (C44.0–C44.9) were used to confirm skin as the primary site. Analyses were restricted to invasive cancers. Individuals were not censored at their first skin cancer diagnosis and could develop additional malignant skin tumors.

We assessed risk for each skin cancer type in PLWH compared with the general population by calculating the standardized incidence ratio (SIR), defined as the ratio of observed to expected cancer counts. Expected counts were determined using general population cancer rates stratified by sex, 5-year age group, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic), calendar year, and cancer registry. We addressed the possible contribution of severe immunosuppression to skin cancer risk by stratifying SIR calculations by history of prior AIDS diagnosis. For this analysis, person-time was categorized into HIV-only

follow-up (prior to AIDS and including the month of AIDS diagnosis) and AIDS follow-up (starting one month after AIDS diagnosis).

Risk factors for various NKSCs were assessed using Poisson regression. We report univariate IRRs in our data supplement (Supplementary Tables S2 and S3) and report multivariate incidence rate ratios (IRRs) as our primary results (Tables 3 and 4). Multivariate models included variables for race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic), calendar year (1996–2002, 2003–2010, 2011–2018), attained age (0–39, 40–49, 50–59, and ≥60 years), sex and HIV risk group (men who have sex with men [MSM], male people who inject drugs [PWID], male other/unknown, female PWID, and female other/unknown), and measures of immunosuppression (attained time since HIV diagnosis and severity of immunosuppression as captured by prior AIDS diagnosis). The MSM risk group included MSM who inject drugs, and the male PWID risk group excluded MSM who inject drugs. When estimating associations with sex, we excluded HIV risk group from our multivariate models, since sex and HIV risk group were colinear, and adjusted for the other variables listed above.

For the most common skin malignancies, we compared the observed number of cases with the expected number based on body surface area, which can be suggestive of UVR-related carcinogenesis when there is an excess of cases on chronically sun-exposed skin of the head and neck (Sargen et al. 2022; Sargen et al. 2020). Observed to expected (O:E) ratios are reported by body site (head and neck, topography codes C44.0–C44.4; trunk, C44.5; upper extremities, C44.6; lower extremities, C44.7). Expected counts were estimated by multiplying the total number of cases at all sites by the proportional body surface area (body surface area estimates according to Wallace's Rule of Nines: head and neck 9%, trunk 37%, upper extremities 18%, lower extremities 36%)(Sargen et al. 2020). Tumors occurring on unknown or overlapping body sites were excluded from this analysis. Binomial confidence intervals were calculated for the O:E ratios, unless there were zero observed cases, in which case an exact method was used.

All statistical analyses were performed using Stata, version 17.0 (StataCorp LLC, College Station, TX). Tests were two-sided and SIR estimates were determined to be significant if $P<0.002$ based on a Bonferroni correction (0.05/27 skin cancer types = 0.002). IRR estimates were significant if $P<0.05$.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

Datasets related to this article cannot be made available to outside researchers due to data use restrictions of HIV and cancer registries.

Abbreviations:

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
DLBCL	Diffuse large B-cell lymphoma
HIV	Human immunodeficiency virus
IRR	Incidence rate ratio
KS	Kaposi Sarcoma
KSHV	Kaposi Sarcoma-associated herpesvirus
MCC	Merkel cell carcinoma
MCPyV	Merkel cell polyomavirus
MSM	Men who have sex with men
NKSC	Nonkeratinocyte skin cancer
O:E	Observed to expected ratio
PLWH	People living with HIV
SIR	Standardized incidence ratio
UVR	Ultraviolet radiation

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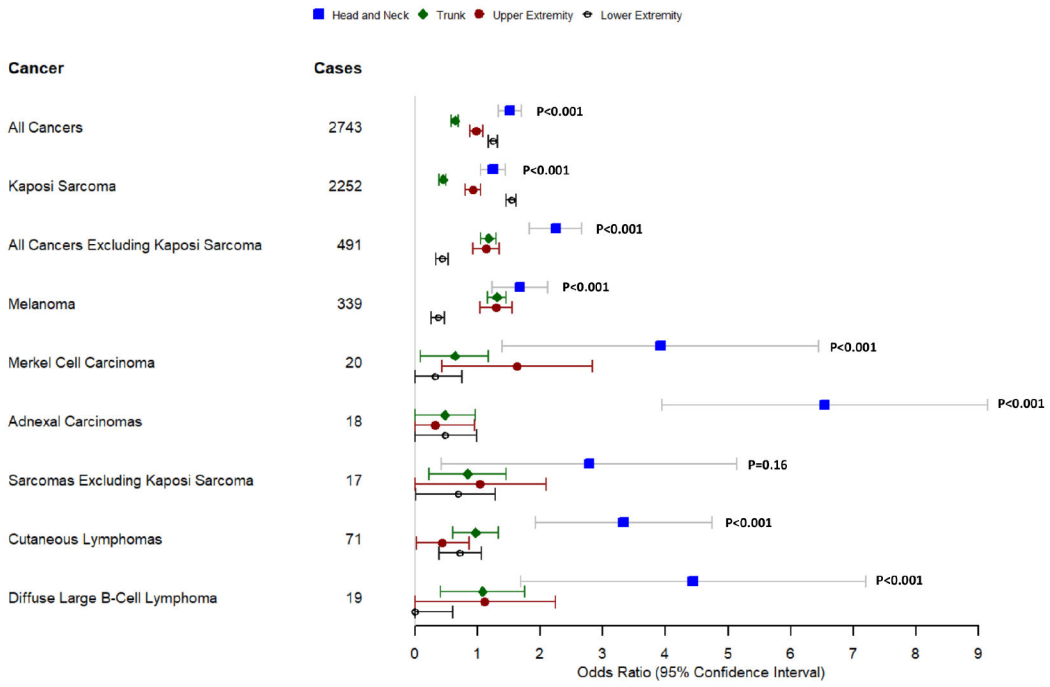

Figure 1. Observed to Expected (O:E) Ratios by Body Site for Nonkeratinocyte Skin Cancers in People Living with HIV.

Observed to expected (O:E) ratios with 95% confidence intervals were calculated by body site and expected counts were estimated by multiplying the total number of cases at all sites by the proportional body surface area. Tumors associated with unknown or overlapping body sites were excluded from this analysis. Binomial confidence intervals were calculated for the O:E ratios, except where zero observed cases were observed, for which an exact method was used. Chi-squared analyses were used to calculate the global P-value.

Table 1.

Demographic and HIV-related Characteristics of People Living with HIV in the United States, 1996–2018.

Characteristic	Number of People Living with HIV (%)
Total	585,706 (100%)
Sex	
Male	426,159 (72.8%)
Female	159,547 (27.2%)
Sex and Risk Group	
MSM	240,252 (41.0%)
Male PWID	66,903 (11.4%)
Male Other/Unknown	119,004 (20.3%)
Female Other/Unknown	125,495 (21.4%)
Female PWID	34,052 (5.8%)
Race/Ethnicity	
Non-Hispanic White	139,789 (23.9 %)
Non-Hispanic Black	304,010 (51.9 %)
Hispanic	141,907 (24.2%)
Age at HIV Diagnosis, Years	
0–39	342,190 (58.4%)
40–49	121,396 (20.7%)
50–59	44,924 (7.7%)
60+	13,057 (2.2%)
Missing	64,139 (11.0%)
AIDS Status	
Never Developed AIDS	225,883 (38.6%)
AIDS Diagnosis Before Entry or During Follow-up	359,823 (61.4%)
Calendar Period	
Before 1996	107,712 (18.4%)
1996–2002	164,777 (28.1%)
2003–2010	183,544 (31.3%)

Characteristic	Number of People Living with HIV (%)
2011–2018	65,534 (11.2%)
HIV Registry [1]	
Colorado	15,149 (2.6%)
Connecticut	13,676 (2.3%)
Washington, D.C.	20,619 (3.5%)
Georgia	52,402 (8.9%)
Louisiana	36,402 (6.2%)
Maryland	30,051 (5.1%)
Michigan	23,193 (4.0%)
New Jersey	51,032 (8.7%)
New York	163,403 (27.9%)
North Carolina	43,807 (7.5%)
Puerto Rico	26,737 (4.6%)
Texas	109,235 (18.7%)

Abbreviations: HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; MSM, men who have sex with men; PWID, people who inject drugs

[1]Nonkeratinocyte skin cancer data was available for the following study sites (calendar years): Colorado (1998–2015), Connecticut (2002–2016), Washington, D.C. (2007–2015), Georgia (2004–2012), Louisiana (1996–2016), Maryland (2008–2018), Michigan (1996–2015), New Jersey (1996–2012), New York (2001–2012), North Carolina (1996–2014), Puerto Rico (2003–2017), Texas (1999–2015).

Table 2.

Standardized Incidence Ratios Comparing Skin Cancer Risk among People Living with HIV to the General Population.

	Total HIV Population			AIDS Population			HIV-Only Population		
Cancer Type	**Observed Cases**	**SIR (95%CI)**	**P-value[1]**	**Observed Cases**	**SIR (95%CI)**	**P-value[1]**	**Observed Cases**	**SIR (95%CI)**	**P-value[1]**
Kaposi Sarcoma	2252	147 (141 −153)	<0.001	1819	177 (169–185)	<0.001	433	86.2 (78.2–94.7)	<0.001
All Skin Cancer Types Excluding Kaposi Sarcoma	491	0.98 (0.90–1.07)	0.72	314	1.00 (0.90–1.12)	0.97	177	0.95 (0.81–1.10)	0.50
Melanoma	339	0.88 (0.79–0.97)	0.01	206	0.85 (0.74–0.98)	0.02	133	0.92 (0.77–1.09)	0.34
Superficial Spreading Melanoma	88	0.78 (0.63–0.96)	0.02	47	0.70 (0.51–0.93)	0.01	41	0.90 (0.65–1.23)	0.58
Lentigo Maligna Melanoma	10	0.66 (0.32–1.21)	0.22	7	0.72 (0.29–1.49)	0.50	3	0.54 (0.11–1.58)	0.39
Nodular Melanoma	27	1.02 (0.67–1.48)	0.98	17	1.02 (0.59–1.63)	1.00	10	1.02 (0.49–1.88)	1.00
Acral Lentiginous Melanoma	9	1.25 (0.57–2.38)	0.59	8	1.72 (0.74–3.39)	0.20	1	0.39 (0.01–2.20)	0.56
Desmoplastic Melanoma	6	1.86 (0.68–4.06)	0.22	1	0.50 (0.01–2.81)	0.82	5	4.04 (1.31–9.42)	0.02
Malignant Melanoma, NOS	191	0.90 (0.77–1.03)	0.14	120	0.88 (0.73–1.06)	0.19	71	0.92 (0.72–1.16)	0.51
Other Melanoma Subtypes	8	0.88 (0.38–1.73)	0.88	6	1.03 (0.38–2.23)	1.00	2	0.61 (0.07–2.21)	0.73
Merkel Cell Carcinoma	20	3.15 (1.93–4.87)	<0.001	15	3.51 (1.96–5.79)	<0.001	5	2.41 (0.78–5.63)	0.12
Adnexal Cancers	18	1.58 (0.94–2.50)	0.08	15	2.01 (1.12–3.31)	0.02	3	0.77 (0.16–2.26)	0.92
Sebaceous Carcinoma	5	1.24 (0.40–2.90)	0.75	5	1.86 (0.60–4.34)	0.27	0	No Estimate	
Sclerosing Sweat Duct Carcinoma	1	1.18 (0.03–6.59)	1.00	1	1.88 (0.05–10.5)	0.83	0	No Estimate	
Eccrine Adenocarcinoma	2	1.71 (0.21–6.16)	0.65	2	2.58 (0.31–9.33)	0.36	0	No Estimate	
Eccrine Poroma	4	3.26 (0.89–8.35)	0.07	4	4.88 (1.33–12.5)	0.02	0	No Estimate	
Ceruminous Adenocarcinoma	1	9.02 (0.23–50.3)	0.21	0	No Estimate		1	22.5 (0.57–125)	0.09
Mucinous Adenocarcinoma	1	0.71 (0.02–4.00)	1.00	1	1.10 (0.03–6.10)	1.00	0	No Estimate	
Apocrine Adenocarcinoma	1	1.51 (0.04–8.46)	0.97	1	2.36 (0.06–13.2)	0.69	0	No Estimate	
Adenoid Cystic Carcinoma	1	1.41 (0.04–7.88)	1.00	1	2.14 (0.05–11.9)	0.75	0	No Estimate	
Skin Appendage Carcinoma	2	1.64 (0.20–5.91)	0.69	0	No Estimate		2	4.65 (0.56–16.8)	0.14
Sarcomas	17	0.82 (0.52–1.23)	0.39	15	0.90 (0.50–1.48)	0.80	8	0.70 (0.30–1.38)	0.40
Dermatofibrosarcoma Protuberans	14	0.56 (0.30–0.93)	0.02	8	0.54 (0.23–1.06)	0.08	6	0.58 (0.21–1.26)	0.22
Cutaneous Leiomyosarcoma	2	1.43 (0.17–5.15)	0.82	2	2.22 (0.27–8.01)	0.46	0	No Estimate	
Lymphangiosarcoma	1	163 (4.12–906)	0.01	0	No Estimate		1	478 (12.1–2660)	<0.001

	Total HIV Population			AIDS Population			HIV-Only Population		
Cancer Type	**Observed Cases**	**SIR (95%CI)**	**P-value[1]**	**Observed Cases**	**SIR (95%CI)**	**P-value[1]**	**Observed Cases**	**SIR (95%CI)**	**P-value[1]**
Lymphomas	71	1.31 (1.02–1.65)	0.03	51	1.48 (1.10–1.95)	0.01	20	1.01 (0.62–1.56)	1.00
T-Cell Lymphomas	49	0.99 (0.73–1.31)	1.00	33	1.05 (0.72–1.47)	0.83	16	0.88 (0.51–1.44)	0.73
Mycosis Fungoides	25	0.77 (0.50–1.14)	0.22	15	0.74 (0.41–1.22)	0.28	10	0.83 (0.40–1.53)	0.68
Anaplastic Large Cell Lymphoma	1	1.06 (0.03–5.93)	1.00	1	No Estimate		0	No Estimate	
CD30+ T-Cell Lymphoma	8	1.96 (0.85–3.87)	0.11	7	2.64 (1.06–5.43)	0.04	1	0.70 (0.02–3.92)	1.00
Extranodal NK/T Cell Lymphoma	1	5.05 (0.13–28.2)	0.36	0	No Estimate		1	15.3 (0.39–85.3)	0.13
Adult T-Cell Leukemia/Lymphoma	1	3.80 (0.10–21.2)	0.46	1	5.39 (0.14–30.0)	0.34	0	No Estimate	
T-cell Lymphoma, NOS	13	1.11 (0.59–1.89)	0.79	9	1.19 (0.54–2.25)	0.70	4	0.96 (0.26–2.47)	1.00
B-cell Lymphomas	22	4.77 (2.99–7.23)	<0.001	18	6.08 (3.60–9.61)	<0.001	4	2.43 (0.66–6.21)	0.17
Diffuse Large B-Cell Lymphoma	19	5.19 (3.13–8.11)	<0.001	17	7.12 (4.15–11.4)	<0.001	2	1.57 (0.19–5.69)	0.73
Follicle Center Lymphoma	3	3.16 (0.65–9.22)	0.14	1	1.75 (0.04–9.73)	0.87	2	5.29 (0.64–19.1)	0.11

Abbreviations: HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; SIR, standardized incidence ratio; CI, confidence interval; NOS, not otherwise specified

[1]SIR estimates were determined to be significant if P<0.002 based on a Bonferroni correction (0.05/27 skin cancer types = 0.002).

Table 3.

Risk of Kaposi Sarcoma in People Living with HIV.

	No. (%)	IRR (95%CI)[1]	P-value
Characteristic			
Total	2252 (1.00)		
Sex			
Male	2092 (0.93)	5.17 (4.40–6.08)	<0.001
Female	160 (0.07)	Reference	
Sex and Risk Group			
MSM	1602 (0.71)	9.84 (7.96–12.2)	<0.001
Male PWID	172 (0.08)	3.38 (2.61–4.36)	<0.001
Male Other/U nknown	318 (0.14)	4.02 (3.19–5.08)	<0.001
Female Other/U nknown	91 (0.04)	Reference	
Female PWID	69 (0.03)	2.48 (1.81–3.40)	<0.001
Race/Ethnicity			
Non-Hispanic White	618 (0.27)	Reference	
Non-Hispanic Black	1086 (0.48)	1.31 (1.18–1.45)	<0.001
Hispanic	548 (0.24)	1.15 (1.02–1.29)	0.02
Calendar Year			
1996–2002	533 (0.24)	Reference	
2003–2010	1178 (0.52)	0.72 (0.65–0.80)	<0.001
2011–2018	541 (0.24)	0.53 (0.47–0.60)	<0.001
Trend			<0.001
Attained Age, Years			
0–39	1078 (0.48)	Reference	
40–49	807 (0.36)	0.70 (0.64–0.77)	<0.001
50–59	297 (0.13)	0.46 (0.40–0.53)	<0.001
60+	70 (0.03)	0.33 (0.26–0.43)	<0.001
Trend			<0.001

	No. (%)	IRR (95%CI)[1]	P-value
Attained Time Since HIV Diagnosis, Years [2]			
≤5	845 (0.38)	Reference	
5.01–10	665 (0.3)	0.74 (0.67–0.82)	<0.001
10.01–15	310 (0.14)	0.54 (0.48–0.62)	<0.001
>15	160 (0.07)	0.45 (0.38–0.54)	<0.001
Missing	272 (0.12)	0.66 (0.57–0.76)	<0.001
Trend			<0.001
AIDS Status			
HIV-Only	433 (0.19)	Reference	
AIDS	1819 (0.81)	3.60 (3.23–4.01)	<0.001

Abbreviations: HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; IRR, incidence rate ratio; CI, confidence interval; MSM, men who have sex with men; PWID, people who inject drugs

[1]IRRs were derived from a multivariate model that included all of the variables in the table, except sex. The IRR for sex was derived from a separate multivariate model that included adjustment for race/ethnicity, attained age, attained time since HIV diagnosis, calendar year, and AIDS status.

[2]Cases with missing information regarding attained time since HIV diagnosis were excluded from multivariate trend analysis.

Table 4.

Risk of Melanoma, Merkel Cell Carcinoma, and Lymphoma in People Living with HIV.

Cancer Type	Melanoma			Merkel Cell Carcinoma			Lymphoma[2]		
Characteristic	**No. (%)**	**IRR (95%CI)[1]**	**P-value**	**No. (%)**	**IRR (95%CI)[1]**	**P-value**	**No. (%)**	**IRR (95%CI)[1]**	**P-value**
Total	339 (1.00)			20 (1.00)			71 (1.00)		
Sex									
Male	291 (0.86)	1.20 (0.88–1.64)	0.25	18 (0.90)	2.81 (0.36–21.9)	0.33	54 (0.76)	1.11 (0.63–1.93)	0.72
Female	48 (0.14)	Reference		2 (0.10)	Reference		17 (0.24)	Reference	
Sex and Risk Group									
MSM	221 (0.65)	1.29 (0.90–1.86)	0.17	13 (0.65)	3.23 (0.40–25.9)	0.27	32 (0.45)	1.26 (0.63–2.53)	0.51
Male PWID	15 (0.04)	0.56 (0.31–1.03)	0.06	3 (0.15)	3.38 (0.34–33.2)	0.30	5 (0.07)	0.52 (0.18–1.49)	0.22
Male Other/U nknown	55 (0.16)	1.18 (0.77–1.80)	0.44	2 (0.10)	1.60 (0.14–17.7)	0.70	17 (0.24)	1.42 (0.68–2.98)	0.36
Female Other/U nknown	36 (10.6)	Reference		1 (0.05)	Reference		12 (0.17)	Reference	
Female PWID	12 (0.04)	0.91 (0.47–1.76)	0.78	1 (0.05)	2.83 (0.17–45.8)	0.46	5 (0.07)	1.11 (0.39–3.18)	0.85
Race/Ethnicity									
Non-Hispanic White	280 (0.83)	Reference		14 (0.70)	Reference		23 (0.32)	Reference	
Non-Hispanic Black	29 (0.09)	0.06 (0.04–0.09)	<0.001	3 (0.15)	0.16 (0.04–0.61)	0.01	32 (0.45)	0.82 (0.46–1.46)	0.50
Hispanic	30 (0.09)	0.13 (0.09–0.19)	<0.001	3 (0.15)	0.27 (0.07–0.99)	0.05	16 (0.23)	0.85 (0.44–1.65)	0.63
Calendar Year									
1996–2002	36 (0.11)	Reference		2 (0.10)	Reference		20 (0.28)	Reference	
2003–2010	174 (0.51)	1.15 (0.80–1.66)	0.45	9 (0.45)	0.88 (0.18–4.25)	0.87	34 (0.48)	0.40 (0.23–0.71)	0.002
2011–2018	129 (0.38)	1.09 (0.73–1.61)	0.68	9 (0.45)	0.95 (0.18–4.96)	0.95	17 (0.24)	0.30 (0.15–0.60)	0.001
Trend			0.92			1.00			0.001
Attained Age, Years									
0–39	46 (0.14)	Reference		0 (0)	Reference[3]		16 (0.23)	Reference	
40–49	96 (0.28)	1.77 (1.23–2.53)	0.002	5 (0.25)			29 (0.41)	1.84 (0.98–3.44)	0.06
50–59	111 (0.33)	3.29 (2.29–4.72)	<0.001	6 (0.30)	2.90 (0.84–10.0)	0.09	19 (0.27)	2.20 (1.09–4.45)	0.03
60+	86 (0.25)	7.15 (4.88–10.5)	<0.001	9 (0.45)	12.6 (3.88–40.8)	<0.001	7 (0.10)	2.37 (0.94–5.97)	0.07
Trend			<0.001			<0.001			0.02

Cancer Type	Melanoma			Merkel Cell Carcinoma			Lymphoma[2]		
Characteristic	**No. (%)**	**IRR (95%CI)[1]**	**P-value**	**No. (%)**	**IRR (95%CI)[1]**	**P-value**	**No. (%)**	**IRR (95%CI)[1]**	**P-value**
Attained Times Since HIV Diagnosis, Years[4]									
≤5	96 (0.28)	Reference		4 (0.20)	Reference		22 (0.31)	Reference	
5.01–10	77 (0.23)	0.63 (0.46–0.85)	0.003	2 (0.10)	0.36 (0.07–1.99)	0.24	19 (0.27)	0.78 (0.42–1.46)	0.45
10.01–15	53 (0.16)	0.51 (0.36–0.72)	<0.001	3 (0.15)	0.58 (0.12–2.73)	0.49	14 (0.20)	0.87 (0.43–1.76)	0.70
>15	67 (0.20)	0.61 (0.43–0.86)	0.005	6 (0.30)	0.97 (0.23–3.99)	0.96	6 (0.08)	0.54 (0.20–1.43)	0.21
Missing	46 (0.14)	0.59 (0.41–0.86)	0.006	5 (0.25)	1.12 (0.27–4.58)	0.88	10 (0.14)	0.82 (0.37–1.80)	0.62
Trend			0.001			0.28			0.24
AIDS Status									
HIV-Only	133 (0.39)	Reference		5 (0.25)	Reference		20 (0.28)	Reference	
AIDS	206 (0.61)	1.04 (0.83–1.30)	0.75	15 (0.75)	1.51 (0.53–4.35)	0.44	51 (0.72)	1.70 (1.00–2.91)	0.05

Abbreviations: HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; IRR, incidence rate ratio; CI, confidence interval; MSM, men who have sex with men; PWID, people who inject drugs

[1]Multivariate models were adjusted for the variables in the above table, except sex. The IRR for sex was derived from a separate multivariate model that included adjustment for race/ethnicity, attained age, attained time since HIV diagnosis, calendar year, and AIDS status.

[2]This category includes all cutaneous lymphomas (T- and B-cell).

[3]For multivariate analysis of MCC, the reference age group was <50 years due to few cases in age groups 0–39 and 40–49.

[4]Cases with missing information regarding attained time since HIV diagnosis were excluded from multivariate trend analysis.