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ARTICLE

HIV Infection Status, Immunodeficiency, and the Incidence of Non-Melanoma Skin Cancer

Michael J. Silverberg, Wendy Leyden, E. Margaret Warton, Charles P. Quesenberry Jr., Eric A. Engels, Maryam M. Asgari

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Correspondence to: Michael J. Silverberg, PhD, MPH, Kaiser Permanente, Division of Research, 2000 Broadway, Oakland, CA 94612 (e-mail: michael.j.silverberg@kp.org).

Background The incidence of non-melanoma skin cancers (NMSCs), including basal cell (BCC) or squamous cell carcinoma (SCC), is not well documented among HIV-positive (HIV$^+$) individuals.

Methods We identified 6560 HIV$^+$ and 36 821 HIV-negative (HIV$^-$) non-Hispanic white adults who were enrolled and followed up in Kaiser Permanente Northern California from 1996 to 2008. The first biopsy-proven NMSCs diagnosed during follow-up were identified from pathology records. Poisson models estimated rate ratios that compared HIV$^+$ (overall and stratified by recent CD4 T-cell counts and serum HIV RNA levels) with HIV$^-$ subjects and were adjusted for age, sex, smoking history, obesity diagnosis history, and census-based household income. Sensitivity analyses were adjusted for outpatient visits (ie, a proxy for screening). All statistical tests were two-sided.

Results The NMSC incidence rate was 1426 and 766 per 100 000 person-years for HIV$^+$ and HIV$^-$ individuals, respectively, which corresponds with an adjusted rate ratio of 2.1 (95% confidence interval [CI] = 1.9 to 2.3). Similarly, the adjusted rate ratio for HIV$^+$ vs HIV$^-$ subjects was 2.6 (95% CI = 2.1 to 3.2) for SCCs, and it was 2.1 (95% CI = 1.8 to 2.3) for BCCs. There was a statistically significant trend of higher rate ratios with lower recent CD4 counts among HIV$^+$ subjects compared with HIV$^-$ subjects for SCCs ($P_{trend} < .001$). Adjustment for number of outpatient visits did not affect the results.

Conclusion HIV$^+$ subjects had a twofold higher incidence rate of NMSCs compared with HIV$^-$ subjects. SCCs but not BCCs were associated with immunodeficiency.

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Non-melanoma skin cancers (NMSCs), which consist of basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs), are the most common cancers in the United States, with more than 3.5 million new cases diagnosed each year (1). Although most NMSCs are easily cured, many become locally invasive and destructive. NMSCs rarely metastasize, but when they do, prognosis is poor (2,3). NMSCs also contribute a substantial economic burden, with estimates suggesting that treatment and management of NMSCs cost the American health-care system more than $2 billion annually (4).

HIV-positive (HIV$^+$) individuals may be particularly vulnerable to NMSCs, given the well-established elevated risk of NMSCs in other immunocompromised populations, including solid organ transplant recipients (5–11), and in those with a history of other cancers (12,13). Also, in the United States, many HIV$^+$ individuals are white and non-Hispanic and may have higher baseline risk of NMSC (14). It is also possible that the predominant group at risk of HIV in the United Sates—men who have sex with men (MSM)—may tend to engage in behaviors, including recreational sun exposure and/or use of tanning beds, that increase their risk for NMSCs (15,16). Finally, given the increasing longevity for HIV$^+$ individuals during the antiretroviral therapy (ART) era, the burden of many age-related non–AIDS-defining cancers, including NMSCs, will only continue to increase (17).

HIV and cancer registry linkage studies have provided ample evidence for the elevated risks of certain cancer types, particularly cancers with known viral etiologies, among HIV$^+$ individuals (11,18). However, it is unclear whether the same holds true for NMSCs because these cancers are not typically reported to cancer registries. The few studies of NMSCs in HIV$^+$ individuals (14,19,20) have lacked appropriate HIV-negative (HIV$^-$) comparison groups, do not distinguish between SCCs and BCCs, or have not evaluated the role of HIV-specific factors, such as immunodeficiency, or tumor-specific factors.

We evaluated NMSC incidence rates in a large cohort of HIV$^+$ and HIV$^-$ subjects who received care in the same health-care system. We compared SCC and BCC rates by HIV status with adjustment for several skin cancer risk factors. We also examined associations between HIV infection and tumor characteristics, including invasiveness, differentiation, and tumor location. Finally, we evaluated

the associations between ART, immunodeficiency, and HIV virus replication on NMSC incidence rates.

Methods

Study Design, Setting, and Participants

We conducted a cohort study from 1996 to 2008 of HIV$^+$ and HIV$^-$ non-Hispanic white adults who were members of Kaiser Permanente Northern California (KPNC), a large integrated health-care delivery system. All KPNC health plan members have access to primary care and comprehensive specialty services, including dermatology. Clinical information is recorded in an electronic medical record. HIV$^+$ subjects were identified from an HIV registry that includes all known cases among KPNC health plan members since 1980. HIV infection was confirmed by medical chart review and by review of case lists with local clinical staff for accuracy.

The study population here consists of a subset of a previously described cohort of adult HIV$^+$ and matched HIV$^-$ individuals within KPNC (18). As described in the prior study (18), health plan members without HIV infection were frequency-matched 10:1 to the HIV$^+$ group by year of start of follow-up, age at start of follow-up (5-year age groups), sex, and medical center. For this study, we restricted the cohort to non-Hispanic white adults because of 1) the comparatively low risk of skin cancer among other racial/ethnic groups and 2) the predominance of non-Hispanic whites among HIV$^+$ individuals in KPNC. The final study population therefore consisted of 6560 HIV$^+$ and 36 821 HIV$^-$ subjects. The ratio of HIV$^-$ to HIV$^+$ subjects in our study population was less than 10:1 after study exclusions because of the higher percentage of non-white racial/ethnic groups and unknown race/ethnicity in the original HIV$^-$ cohort (18).

The index date for HIV$^+$ subjects was defined as the earliest date after January 1, 1996, when they met all of the following criteria: KPNC member, aged 18 years or older, known to be HIV$^+$, and in HIV care, defined as the first CD4 T-cell count measurement recorded in the health system. The index date for HIV$^-$ subjects was defined as the earliest date during the year selected in frequency-matching when they met the following criteria: KPNC member and aged 18 years or older. Subjects were followed up from the index date until the date of NMSC diagnosis, loss to follow-up, or December 31, 2008, whichever occurred first.

NMSC Ascertainment

The outcome of interest was the first occurrence of an NMSC, defined as a BCC or SCC. Separate analyses were also performed for BCC and SCC subtypes. Subjects who experienced both subtypes during follow-up were counted as having events for both the BCC and SCC analyses; however, only the first of these diagnoses was considered for the overall NMSC analysis. Malignant melanoma and other rare types of skin cancers, such as Merkel cell or adnexal carcinomas, were not included.

All biopsy-proven NMSC diagnoses since 1996 are recorded in a research NMSC registry maintained at the Division of Research at KPNC. Potential NMSC cases were identified from an electronic database of pathology reports included in the KPNC electronic medical record. The pathology database includes information on all pathology specimens received for examination from KPNC medical facilities. Information in the pathology database includes the date and type of clinical specimen, tumor location, tumor subtype, and gross and microscopic diagnoses (in text format).

For this study, the pathology reports for all potential BCC and SCC cases were identified by performing an electronic text string search for the following terms: "skin," "dermis," and "dermal," to identify text related to skin; "basal," "basal cell," "BCC," and "epithelioma," to identify text related to BCCs; "squamous," "SCC," "bowen," and "squam," to identify text related to SCCs; "baso" and "basaloid," to identify text related to basosquamous carcinoma; and "rule out," "rule-out," "RO," and "R/O," to identify text related to ruling out a particular diagnosis. Next, all potential cases identified by text strings were further reviewed and confirmed by the study dermatologist (M. M. Asgari). Tumor invasiveness (classified as superficial or invasive) was also collected during review of pathology reports. Superficial tumors included superficial BCCs (21) and squamous cell carcinoma in situ. Tumor differentiation was also collected from pathology reports for SCCs only. The degree of differentiation of a cutaneous SCC is rendered by the pathologist and is part of the pathology report. Although SCCs do not have an established grading system, malignancies are typically graded with respect to differentiation as poor, moderate, and well by pathologists (22). In cases where the pathologist rendered two descriptive adjectives for the degree of differentiation (eg, "moderate-to-well" or "poor-to-moderate") the tumor was assigned to the least differentiated category (ie, "moderate-to-well" would be classified as a "moderate" tumor). Finally, anatomic location (ie, head or neck, arms or legs, trunk or buttocks) was also collected from the pathology report. For analysis, head or neck and arms or legs were considered sun-exposed locations and trunk or buttocks were considered non–sun-exposed locations.

Other Data Sources

Data elements obtained from the KPNC HIV registry included sex, race/ethnicity, HIV transmission risk factor, duration of known HIV infection, and date of death. Other data obtained from the electronic medical record included laboratory test results (CD4 counts and HIV RNA levels); pharmacy prescription fills (antiretrovirals); demographics (age, sex, and income levels based on 2000 Census tract data); health plan enrollment periods; clinical diagnoses, including overweight or obesity diagnoses [International Classification of Diseases, revision 9 (ICD-9) codes (23): 278, 259.9, V85; KP-specific weight/height codes recorded during outpatient visits]; tobacco use (ICD-9 305.1, V15, V65, 649, and KP-specific tobacco use codes recorded during outpatient visits); and number of outpatient visits, both overall and to dermatology departments.

The institutional review board at KPNC approved the study, providing waivers of informed written consent.

Statistical Analysis

Variables considered in the analysis included age (<40, 40–49, 50–64, ≥65 years), sex, smoking history (ever/never), overweight/obesity diagnosis history (ever/never), and 2000 Census-based income levels (quintiles). Additionally, among HIV$^+$ subjects only,

we considered any prior ART use, years known to be HIV+ (≥10, 5–9.9, <5 years), HIV transmission risk factor (MSM, heterosexual sex, injection drug use, unknown), recent (ie, within prior 6 months) CD4 counts (<200, 200–499, ≥500 cells/μL), and recent HIV RNA levels (≥10 000, 500–9999, <500 copies/mL). Cutoffs for age, years known to be HIV+, CD4 counts, and HIV RNA levels were chosen a priori based on our prior experience given the distribution of these variables in our population (18). Time-dependent variables included age, prior ART use, years known to be HIV+, and recent CD4 counts and HIV RNA levels; all other variables were treated as fixed. All time-dependent variables were updated continuously except for CD4 counts and HIV RNA levels, which were updated at 6-month intervals, which corresponds with the usual clinical approach for the measurement of these laboratory measures.

We first compared demographic and clinical characteristics of HIV+ and HIV− subjects at the start of follow-up using the Pearson χ^2 test for categorical variables and the Kruskal–Wallis test for continuous variables. Among subjects with an NMSC diagnosis, we compared tumor characteristics by HIV status.

We next computed NMSC incidence rates per 100 000 person-years by HIV status. Adjusted rate ratios (RRs) for HIV status were obtained from Poisson regression models that included terms for HIV status, age, sex, smoking, overweight/obesity, and 2000 Census-based income levels. Separate multivariable models were fit for outcomes of any NMSC, any BCC, and any SCC. In addition, separate models were fit for outcomes defined by invasiveness (ie, invasive and superficial) and anatomic location (ie, sun-exposed and non–sun-exposed). For the outcome of SCC only, we also fit a model for well-differentiated SCCs; other differentiation levels were not common enough for separate analysis. In multivariable models, NMSCs with unknown invasiveness, differentiation level, or anatomic location were considered censoring events. Finally, we considered whether there was a sex–HIV status interaction for the outcomes of any NMSC, BCC, and SCC. For women, we compared NMSC rates between all HIV+ women and HIV− women (reference group). For men, we compared NMSC rates between HIV+ MSM, other HIV+ men, and HIV− men (reference group).

Next, we compared the incidence rate of NMSCs in HIV+ subjects stratified by recent CD4 count with the incidence rate among HIV− subjects (reference group). This approach allowed for a direct evaluation of whether cancer incidence in HIV+ subjects with a more intact immune system is similar to the NMSC incidence in the general population. A Poisson model included a variable for HIV status and CD4 counts with the following categories: HIV+ subjects with CD4 count less than 200 cells/μL, HIV+ subjects with CD4 count of 201 to 499 cells/μL, HIV+ subjects with CD4 count of 500 or more cells/μL, and HIV− subjects (reference group). The Poisson model additionally adjusted for age, sex, smoking history, overweight/obesity diagnosis history, and 2000 Census-based income levels. We tested for a trend in rate ratios across HIV status and CD4 counts using the likelihood ratio test.

Finally, among HIV+ subjects only, we computed adjusted rate ratios for HIV-specific factors, including recent CD4 count, recent HIV RNA level, prior ART use, HIV exposure risk, and years known to be HIV+, in addition to other factors described above.

We performed a sensitivity analysis to examine whether differential ascertainment of NMSC by HIV status explained the observed results. We first determined the number of outpatient and dermatology visits in prior year for all subjects (time-dependent variable updated on a yearly basis) and reanalyzed primary analyses for HIV status and recent CD4 count by including recent outpatient visits (0, 1, 2, ≥3 visits) as a variable in multivariable models. Because creation of this variable required 1 year of observation, these sensitivity analyses were restricted to subjects with at least 1 year of prior health-plan membership at study baseline.

All analyses were performed with SAS software version 9.1 (SAS Institute, Cary, NC) using the Genmod procedure for Poisson regression. All statistical tests were two-sided, and statistical significance was defined as P less than .05. We also performed model checks to evaluate certain assumptions of the Poisson models. Each model was examined for over- or underdispersion (ie, variance not equal to the mean). We noted no evidence of extra-Poisson variability for any of the models, and inferences were unchanged (data not shown). There was also no evidence for a lack of model fit based on the deviance criterion ($P > .9$ for all models).

Results

We identified 6560 HIV+ subjects contributing 34 219 person-years and 36 821 HIV− subjects contributing 264 761 person-years. Baseline characteristics are presented in Table 1. Compared with HIV− subjects, HIV+ subjects were slightly younger, more likely to be male, more likely to have a history of smoking, less likely to have an overweight/obesity diagnosis, and lived in lower-income Census blocks. HIV+ subjects also had statistically significantly more outpatient ($P < .001$) and dermatology ($P < .001$) visits in the year before baseline compared with HIV− subjects.

HIV+ subjects were diagnosed with 386 BCCs and 136 SCCs (67 had both), which corresponds with a BCC:SCC tumor ratio of 2.8:1. HIV− subjects were diagnosed with 1682 BCCs and 479 SCCs (207 had both), which corresponds with a BCC:SCC tumor ratio of 3.5:1. HIV+ subjects with either BCCs or SCCs were diagnosed at slightly younger ages compared with HIV− subjects (Table 2), which is consistent with the younger overall mean age of the HIV+ cohort. A lower percentage of BCCs were invasive among HIV+ subjects compared with HIV− subjects ($P < .001$). BCCs occurred just as commonly on sun-exposed body locations among HIV+ and HIV− subjects ($P = .81$). However, BCCs were less common on the head and neck and more common on arms and legs for HIV+ subjects compared with HIV− subjects ($P < .001$). For SCCs, tumor invasiveness, differentiation, and location were similar by HIV status ($P > .05$).

Crude incidence rates for NMSCs and adjusted rate ratios are presented in Table 3. Overall, the crude incidence rate for any NMSC was 1426 and 766 per 100 000 person-years for HIV+ and HIV− subjects, respectively, corresponding with an adjusted rate ratio of 2.1 (95% confidence interval [CI] = 1.9 to 2.3). The association of HIV status on NMSC outcome types was most pronounced for superficial NMSCs, with a rate ratio of 2.8 (95% CI = 2.3 to 3.5); rate ratios for HIV status for superficial (RR = 1.9), sun-exposed (RR = 2.1), and non–sun-exposed (RR = 2.2) NMSCs were statistically significant but had lower magnitude associations. Sensitivity analyses that adjusted for recent outpatient visits resulted in a rate ratio for NMSCs of 1.8 (95% CI = 1.6 to 2.0; $P < .001$).

Table 1. Baseline characteristics for HIV-positive and HIV-negative subjects*

Characteristic	HIV-positive	HIV-negative
No.	6560	36 821
Person-years	34 219	264 761
Mean No. years of follow-up (SD)	5.2 (4.4)	7.2 (4.4)
Mean age, y (SD)	42.0 (9.3)	42.8 (10.0)
Male, %	94.0	88.1
Median household income in census block, $	57 148	61 875
Ever history of tobacco smoking, %	48.7	37.4
Ever overweight/obese, %	35.9	49.4
HIV exposure risk		
Men who have sex with men	72.2	—
Injection drug use	8.5	—
Heterosexual	7.8	—
Unknown	11.5	
Mean No. of years known to be HIV-positive (SD)	5.1 (5.1)	—
Any ART use, %	52.4	—
Any combination ART use, %	19.7	—
Mean CD4 counts, T-cells/μL (SD)	365 (269)	—
Mean HIV RNA levels, copies/mL (SD)	65 955 (127 700)	—
Mean No. outpatient visits in prior year (SD)†	12.8 (16.2)	5.4 (10.1)
Mean No. dermatology visits in prior year (SD)†	1.0 (4.5)	0.3 (2.0)

* $P < .001$ (two-sided) for all comparisons of characteristics by HIV status. Test based on Pearson χ^2 test for categorical variables and Kruskal–Wallis test for continuous variables. ART = antiretroviral therapy; SD = standard deviation; —, data not available for HIV-negative subjects.

† Excludes 2537 (39%) HIV-positive subjects and 6314 (17%) HIV-negative subjects with less than 1 year prior health-plan membership.

The crude BCC incidence rates were 1197 and 656 per 100 000 person-years for HIV$^+$ and HIV$^-$ subjects, respectively, corresponding with an adjusted rate ratio of 2.1 (95% CI = 1.8 to 2.3). The association between HIV status and BCC outcome types was more pronounced for superficial BCCs (RR = 3.0, 95% CI = 2.4 to 3.8) than for invasive BCCs (RR = 1.8, 95% CI = 1.6 to 2.1). Rate ratios for BCCs in sun-exposed and non–sun-exposed locations were of similar magnitude. Sensitivity analyses adjusting for recent outpatient visits resulted in a rate ratio for any BCCs of 1.7 (95% CI = 1.5 to 2.0; $P < .001$).

The crude SCC incidence rates were 405 and 182 per 100,000 person-years for HIV$^+$ and HIV$^-$ subjects, respectively, corresponding with an adjusted rate ratio of 2.6 (95% CI = 2.1 to 3.2). The rate ratios for SCC outcome types among HIV$^+$ vs HIV$^-$ subjects were of similar magnitude for superficial and invasive SCCs. However, the rate ratio for non–sun-exposed SCCs (3.4, 95% CI = 2.1 to 5.7) was moderately higher than that for sun-exposed SCCs (2.5, 95% CI = 2.0 to 3.1). Finally, well-differentiated SCCs had a rate ratio of 1.9 (95% CI = 1.3 to 2.9); we did not have sufficient events to evaluate rate ratios for SCCs with poor or moderate differentiation. Sensitivity analyses that adjusted for recent outpatient visits resulted in a rate ratio for any SCCs of 2.1 (95% CI = 1.7 to 2.6; $P < .001$).

Table 4 presents NMSC rate ratios stratified by sex. Among women, there was no difference in the BCC incidence rate by HIV status (RR = 1.1, 95% CI = 0.6 to 2.0), whereas among men, there was a statistically significant higher BCC incidence rate for HIV$^+$ MSM (RR = 2.2, 95% CI = 2.0 to 2.5) and other HIV$^+$ men (RR = 1.6, 95% CI = 1.1 to 2.4) compared with HIV$^-$ men. By contrast, HIV$^+$ women had an increased SCC incidence rate compared with HIV$^-$ women (RR = 2.3, 95% CI = 0.8 to 6.8; $P = .13$), although the rate ratio was not statistically significant. There was a statistically significant increased SCC incidence rate for HIV$^+$ MSM (RR = 2.5, 95% CI = 2.0 to 3.1; P < .001) and other HIV$^+$ men with other risk factors (RR = 3.8, 95% CI = 2.4 to 6.1; P < .001) compared with HIV$^-$ men.

We observed a statistically significant trend of higher rate ratios with lower recent CD4 counts among HIV$^+$ subjects compared with HIV$^-$ subjects for SCCs but not for BCCs (Figure 1). For SCCs, the rate ratio decreased from 4.2 (95% CI = 2.9 to 6.1) to 3.0 (95% CI = 2.3 to 3.8) to 1.6 (95% CI = 1.1 to 2.3) for CD4 counts of less than 200, 200 to 499, and 500 or more cells/μL, respectively ($P_{trend} < .001$). For BCCs, the relationship with recent CD4 count was less pronounced and not statistically significant ($P_{trend} = .13$), with rate ratios of 2.5 (95% CI = 1.9 to 3.2), 2.1 (95% CI = 1.8 to 2.4), and 1.8 (95% CI = 1.5 to 2.2) for CD4 counts of less than 200, 200 to 499, and 500 or more cells/μL, respectively. Sensitivity analyses that adjusted for recent outpatient visits did not change inferences: for SCCs, the trend for lower rate ratios with higher recent CD4 count remained statistically significant ($P_{trend} = .004$), and for BCCs, the trend remained non–statistically significant ($P_{trend} = .13$). The BCC:SCC ratio was 3.5:1 for HIV$^-$ subjects (derived from BCC and SCC case counts for HIV$^-$ subjects in Table 2); for HIV$^+$ subjects, the BCC:SCC ratios were 2.0:1, 2.7:1, and 3.7:1 for those with CD4 counts of less than 200, 200 to 499, and 500 or more cells/μL, respectively (data not shown).

Finally, we evaluated several demographic and clinical characteristics as risk factors for NMSC among HIV$^+$ subjects only (Table 5). Neither prior ART nor recent CD4 count was associated with the incidence of BCC. Although HIV RNA levels of 500 to 9999 copies/mL were associated with an increased incidence rate of BCC, the association was not consistent with a biologic effect, given that higher HIV RNA levels (ie, ≥10 000 copies/mL) were not associated with the incidence of BCCs. Older age and higher household income were associated with increased BCC incidence

Table 2. Age at diagnosis and tumor characteristics for HIV-positive (HIV^+) and HIV-negative (HIV^-) subjects with non-melanoma skin cancer*

	Any NMSC			BCC			SCC		
Characteristic	**HIV^+ (n = 455)**	**HIV^- (n = 1954)**	***P***	**HIV^+ (n = 386)**	**HIV^- (n = 1682)**	***P***	**HIV^+ (n = 136)**	**HIV^- (n = 479)**	***P***
Mean age at diagnosis, y (SD)	48.8 (9.1)	50.4 (9.9)	<.001	48.8 (9.1)	50.4 (9.9)	<.001	48.8 (9.1)	50.4 (9.9)	<.001
Invasiveness, %			.001			<.001			.73
Superficial†	31.4	23.2		31.1	20.4		36.9	35.2	
Invasive	68.6	76.8		68.9	79.6		63.1	64.8	
Unknown invasiveness, %‡	18.0	18.7		20.7	20.0		10.3	10.4	
Differentiation, %§									.19
Poor	n/a	n/a		n/a	n/a		4.3	4.2	
Moderate	n/a	n/a		n/a	n/a		36.2	23.3	
Well	n/a	n/a		n/a	n/a		59.6	72.5	
Unknown differentiation, %‡	n/a	n/a		n/a	n/a		65.4	60.5	
Location, %			.003			<.001			.22
Head/neck	52.8	60.6		51.7	62.3		54.8	53.4	
Arms/legs	24.4	18.1		24.5	14.5		28.9	35.0	
Trunk/buttocks	22.8	21.3		23.8	23.2		16.3	11.6	
Sun-exposed location, %‖	77.2	78.7	.47	76.2	76.8	.81	83.7	88.4	.15
Sun-exposed	22.8	21.3		23.8	23.2		16.3	11.6	
Non–sun-exposed	0.9	0.7		0.8	0.5		0.7	1.0	
Unknown location, %‡									

* *P* values (two-sided) based on χ^2 statistic comparing tumor characteristics by HIV status. BCC = basal cell carcinoma; NMSC = non-melanoma skin cancer; SCC = squamous cell carcinoma; SD = standard deviation; n/a = not applicable.

† Includes superficial multifocal BCC and SCC in situ.

‡ No statistically significant differences by HIV status for percentage with unknown tumor characteristic (all $P > .05$).

§ Differentiation only applicable for SCCs.

‖ Sun-exposed location includes head/neck and arms/legs. Non–sun-exposed location includes trunk/buttocks.

Table 3. Non-melanoma skin cancer incidence rates and rate ratios by HIV status*

Cancer type	HIV-positive		HIV-negative			
	No.	Rate†	No.	Rate†	RR‡ (95% CI)	*P*
Any NMSC	455	1426	1954	766	2.1 (1.9 to 2.3)	<.001
Invasive NMSC	256	778	1220	471	1.9 (1.7 to 2.2)	<.001
Superficial NMSC	117	348	369	140	2.8 (2.3 to 3.5)	<.001
Sun-exposed NMSC	348	1072	1528	594	2.1 (1.8 to 2.3)	<.001
Non–sun-exposed NMSC	103	306	413	157	2.2 (1.8 to 2.7)	<.001
Any BCC	386	1197	1682	656	2.1 (1.8 to 2.3)	<.001
Invasive BCC	211	637	1071	412	1.8 (1.6 to 2.1)	<.001
Superficial BCC	95	281	274	104	3.0 (2.4 to 3.8)	<.001
Sun-exposed BCC	292	892	1285	497	2.1 (1.8 to 2.4)	<.001
Non–sun-exposed BCC	91	270	388	148	2.0 (1.6 to 2.6)	<.001
Any SCC	136	405	479	182	2.6 (2.1 to 3.2)	<.001
Invasive SCC	77	228	278	105	2.5 (2.0 to 3.3)	<.001
Superficial SCC	45	132	151	57	2.8 (2.0 to 3.9)	<.001
Sun-exposed SCC	113	336	419	159	2.5 (2.0 to 3.1)	<.001
Non–sun-exposed SCC	22	64	55	21	3.4 (2.1 to 5.7)	<.001
Well-differentiated SCC	28	82	137	52	1.9 (1.3 to 2.9)	.002

* BCC = basal cell carcinoma; CI = confidence interval; NMSC = non-melanoma skin cancer; RR = rate ratio; SCC = squamous cell carcinoma.

† Crude incidence rate per 100 000 person-years.

‡ Rate ratio from Poisson regression models compares cancer incidence in HIV-positive subjects with HIV-negative subjects (reference group). All models were adjusted for age, sex, smoking, overweight/obesity, and 2000 Census-based income levels.

Table 4. Non-melanoma skin cancer rate ratios by HIV status, sex, and HIV transmission risk*

Strata defined by sex, HIV status, and HIV risk factor	NMSC		BCC		SCC	
	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
Women						
HIV+	1.2 (0.7 to 2.2)	.46	1.1 (0.6 to 2.0)	.85	2.3 (0.8 to 6.8)	.13
HIV−	1.0 (referent)		1.0 (referent)		1.0 (referent)	
Men						
HIV+, MSM	2.2 (1.9 to 2.5)	<.001	2.2 (2.0 to 2.5)	<.001	2.5 (2.0 to 3.1)	<.001
HIV+, other HIV risk†	2.2 (1.6 to 2.9)	<.001	1.6 (1.1 to 2.4)	.009	3.8 (2.4 to 6.1)	<.001
HIV−	1.0 (referent)		1.0 (referent)		1.0 (referent)	

* Rate ratios from sex-stratified Poisson regression models adjusted for age, smoking, overweight/obesity, and 2000 Census-based income levels. BCC = basal cell carcinoma; CI = confidence interval; HIV+ = HIV-positive; HIV− = HIV-negative; MSM = men who have sex with men; NMSC = non-melanoma skin cancer; RR = rate ratio; SCC = squamous cell carcinoma.

† Heterosexual and/or injection drug use HIV transmission risk factor. Men with unknown HIV risk were excluded.

rates, whereas female sex (compared with MSM) was associated with lower incidence rates. Prior ART was not associated with the incidence of SCCs. Consistent with results presented in Figure 1, lower recent CD4 counts were associated with a higher incidence rate of SCCs. Similar to the findings for BCCs, the association of HIV RNA levels with SCCs was not consistent with a biologic effect. Older age was the only other factor associated with SCCs: incidence rates were almost 50 times higher among those older than 65 years compared with those 18 to 39 years of age (RR = 48.5, 95% CI = 16.8 to 140.3).

Discussion

We found that HIV+ subjects had a 2.1-fold higher incidence rate of BCC and 2.6-fold higher incidence rate of SCC compared with HIV− subjects from the same health-care system. The increased incidence rate of BCCs for HIV+ subjects appeared to be limited to men, whereas the increased incidence rate of SCCs was observed for women, HIV+ MSM, and other HIV+ men. Finally, lower recent CD4 counts among HIV+ subjects conferred a higher incidence rate for SCC but not for BCC.

The observed increased incidence rate of NMSCs in HIV+ subjects is consistent with the growing evidence about this population's increased risk for a broad range of cancers (24). In a large meta-analysis, both HIV/AIDS and organ transplant recipient populations exhibited increased incidence for many types of cancer, most with a known or suspected viral cause, including all human papillomavirus (HPV)–related cancers, Epstein–Barr virus–related cancers (non-Hodgkin lymphoma, Hodgkin lymphoma), Kaposi sarcoma (associated with human herpes virus type 8), and liver cancer (associated with viral hepatitis) (11). The increased cancer risk is likely due to immunodeficiency, the main risk factor

Table 5. Risk factors for non-melanoma skin cancer among HIV-positive subjects*

	NMSC		BCC		SCC	
Variable	**RR 95% CI)**	***P***	**RR (95% CI)**	***P***	**RR (95% CI)**	***P***
Prior combination ART	1.0 (0.8 to 1.3)	.86	0.9 (0.7 to 1.2)	.52	1.0 (0.6 to 1.5)	.81
Recent CD4 T-cell counts						
<200 vs ≥500 cells/μL	1.5 (1.1 to 2.0)	.005	1.4 (1.0 to 1.9)	.06	2.4 (1.4 to 4.2)	.001
200–499 vs ≥500 cells/μL	1.2 (0.9 to 1.4)	.21	1.1 (0.9 to 1.4)	.35	1.8 (1.2 to 2.8)	.007
Recent HIV RNA						
≥10 000 vs <500 copies/mL	1.3 (1.0 to 1.7)	.047	1.2 (0.9 to 1.6)	.27	1.4 (0.9 to 2.2)	.20
500–9999 vs <500 copies/mL	1.7 (1.3 to 2.2)	<.001	1.6 (1.2 to 2.1)	<.001	1.8 (1.1 to 2.8)	.02
Sex or HIV transmission risk						
Women vs MSM	0.5 (0.3 to 0.8)	.006	0.4 (0.2 to 0.8)	.005	0.6 (0.2 to 1.5)	.24
Other HIV risk† vs MSM	1.0 (0.7 to 1.4)	.97	0.7 (0.5 to 1.1)	.13	1.6 (1.0 to 2.6)	.08
Men with unknown HIV risk vs MSM	0.8 (0.6 to 1.1)	.20	0.7 (0.5 to 1.0)	.08	0.9 (0.5 to 1.7)	.82
Years known to be HIV-positive						
≥10 vs <5	1.2 (1.0 to 1.6)	.10	1.3 (1.0 to 1.7)	.06	1.3 (0.8 to 2.1)	.28
5–9.9 vs <5	1.3 (1.0 to 1.7)	.06	1.2 (0.9 to 1.7)	.19	1.2 (0.7 to 2.0)	.54
Current age, y						
≥65 vs 18–39	11.8 (7.6 to 18.4)	<.001	9.3 (5.7 to 15.1)	<.001	48.5 (16.8 to 140.3)	<.001
50–64 vs 18–39	5.7 (3.9 to 8.2)	<.001	4.9 (3.3 to 7.2)	<.001	14.3 (5.2 to 39.8)	<.001
40–49 vs 18–39	2.7 (1.9 to 3.9)	<.001	2.6 (1.8 to 3.9)	<.001	5.7 (2.0 to 16.1)	.001
Ever smoked	1.0 (0.8 to 1.2)	.77	1.0 (0.8 to 1.2)	.90	0.9 (0.6 to 1.3)	.52
Ever overweight/obese	1.0 (0.8 to 1.2)	.93	1.0 (0.9 to 1.3)	.71	1.0 (0.7 to 1.4)	.87
Median household income						
Quintile 5 (high) vs 1 (low)	1.3 (1.0 to 1.8)	.07	1.6 (1.2 to 2.3)	.005	1.2 (0.7 to 2.1)	.54
Quintile 4 vs 1 (low)	1.1 (0.8 to 1.4)	.72	1.2 (0.8 to 1.7)	.33	0.8 (0.5 to 1.4)	.47
Quintile 3 vs 1 (low)	1.1 (0.8 to 1.4)	.57	1.2 (0.9 to 1.6)	.28	1.0 (0.6 to 1.6)	.97
Quintile 2 vs 1 (low)	1.3 (1.0 to 1.7)	.11	1.4 (1.0 to 1.9)	.06	1.2 (0.7 to 2.0)	.54

* Rate ratios obtained from Poisson regression models adjusted for all variables listed. *P* values are all two-sided. ART = antiretroviral therapy; BCC = basal cell carcinoma; CI = confidence interval; MSM = men who have sex with men; NMSC = non-melanoma skin cancer; RR = rate ratio; SCC = squamous cell carcinoma

† Heterosexual and/or injection drug use HIV transmission risk factor.

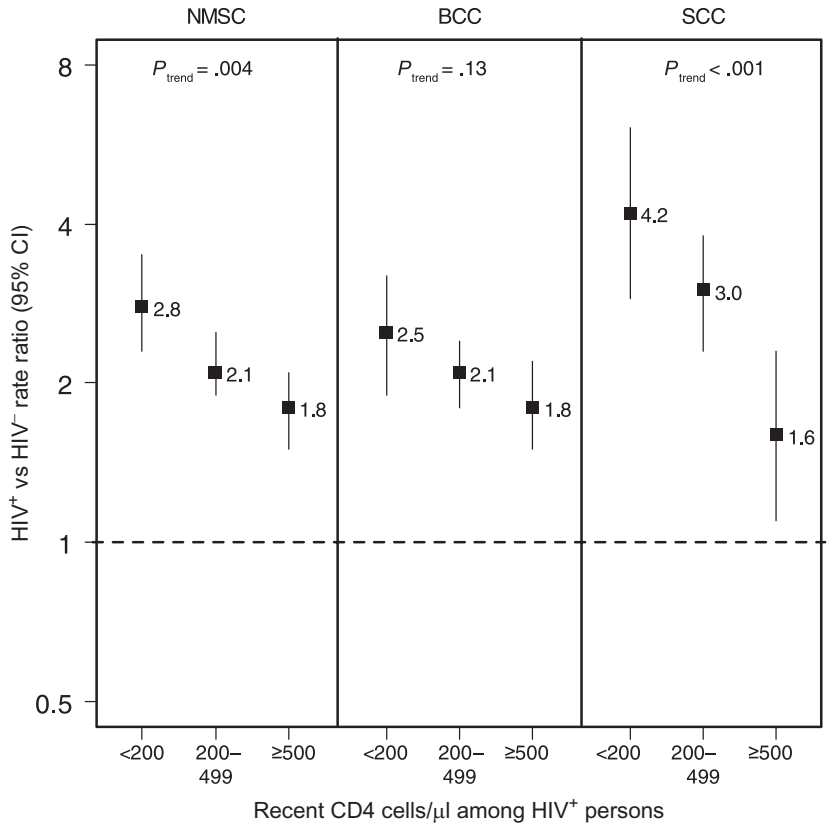

Figure 1. Rate ratios (and 95% confidence intervals [CIs]) for non-melanoma skin cancer by recent CD4 counts among HIV-positive (HIV$^+$) subjects compared with HIV-negative (HIV$^-$) subjects. Rate ratios are from Poisson regression models with terms for HIV status/recent CD4 counts (HIV$^-$ reference), age, sex, smoking, overweight/obesity, and 2000 Census-based income levels. Two-sided *P* value tests trend in rate ratios over CD4 count strata are by the likelihood ratio test. Results are shown separately for non-melanoma skin cancer (NMSC, **left panel**), basal cell carcinoma (BCC, **middle panel**), and squamous cell carcinoma (SCC, **right panel**). The **black squares** correspond with rate ratio point estimates, the **vertical solid lines** correspond with 95% confidence intervals, and the **dashed horizontal line** corresponds with a rate ratio of 1.0.

these populations have in common (11,25). This conclusion was reinforced by a recent large, population-based study of US transplant recipients (26).

It is also well established that solid organ transplants confer a substantially elevated risk of NMSC, with demonstrated increased risks of more than 50-fold (5–11). However, limited data exist about the association between HIV/AIDS and the risk of NMSC, specifically with regard to the risks for BCCs and/or SCCs. Several studies that have used linked data from HIV/AIDS and cancer registries have reported standardized incidence ratios for other nonepithelial skin cancers [International Classification of Diseases for Oncology, Third Edition (27) site code C44, excluding melanoma histologies] that range from 1.8 to 6.5 (11,28–33), whereas other studies have indicated no statistically significant associations with HIV infection (34–36). However, most cancer registries exclude BCCs and SCCs, which are not reportable malignancies. Instead, the small number of cancers reported as nonepithelial skin cancers likely represents a mix of rare cancers such as Merkel cell or adnexal carcinomas. Therefore, these studies do not provide valid estimates of NMSC risk.

A few studies have considered the association between HIV status and the risk of NMSC without relying on cancer registry data. A case–control study among a South African black population diagnosed with cancer compared the prevalence of HIV infection among those diagnosed with cancers identified a priori as possibly related to HIV with the prevalence of HIV infection among individuals with other cancers (20). The authors reported an odds ratio (OR) of 2.6 in a comparison of 70 individuals diagnosed with SCC and 4399 individuals diagnosed with other cancers, which was the highest odds ratio for all cancers studied except for Kaposi sarcoma (OR = 50) and non-Hodgkin lymphoma (OR = 6). It is notable that this result is highly consistent with our reported adjusted rate ratio of 2.6 in our comparison of SCC rates in HIV$^+$ and HIV$^-$ subjects, despite the very different racial/ethnic groups studied.

The most detailed data to date about the incidence of NMSC in HIV$^+$ individuals has been provided by the US Military HIV Natural History Study. Among 4144 HIV$^+$ individuals, Burgi et al. (14) identified 43 BCCs and 16 SCCs among HIV$^+$ individuals, their most commonly diagnosed non–AIDS-defining cancers, corresponding with incidence rates (per 100 000 person-years) of 795 for BCC among white men and 159 and 39 for SCC among white and black men, respectively. Although an internal HIV$^-$ comparison group was not included, Burgi et al. (14) indicated these rates were statistically significantly elevated ($P < .05$) compared with general US population rates.

A recent follow-up study in the same population by Crum-Cianflone et al. (19), which focused only on cutaneous malignancies, is more directly comparable with our study because the authors

specifically excluded skin cancers from mucosal sites, as we have done. In total, they identified 51 BCCs and eight SCCs among HIV+ individuals, with incidence rates after 1996 of 339 and 82 per 100 000 person-years, respectively. The corresponding incidence rates in our study were slightly higher, particularly for SCCs (386 for BCC and 136 for SCC), which might reflect differences in SCC case ascertainment (eg, Crum-Cianflone et al. did not specifically mention Bowen's disease in their case search algorithm). Finally, Crum-Cianflone et al. also presented a multivariable analysis of all cutaneous malignancies as a group (ie, BCCs, SCCs, and malignant melanoma). The authors indicated that only older age and white race/ethnicity were associated with the risk of non–AIDS-defining cutaneous malignancies, whereas CD4 counts, HIV RNA levels, and ART were not associated with an elevated risk of cutaneous malignancies. However, the analysis of the cancer group of all cutaneous malignancies by Crum-Cianflone et al. may have limited comparability with our separate analysis of BCCs and SCCs.

Here, we provide evidence with an internal control group that SCCs and BCCs are both increased approximately twofold among HIV+ subjects and that the observed association with immunodeficiency appears to be specific to SCC and not BCC. It is noteworthy that the observed increased incidence rate here for SCCs among HIV+ subjects is much lower than the more than 50-fold higher rates observed among transplant populations (5–11). Furthermore, SCCs among transplant recipients tend to be very aggressive (37); by contrast, we noted similar clinical presentation for NMSCs by HIV status with respect to invasiveness, differentiation, and location. These observations suggest that immunosuppressive transplant medications may have direct oncogenic properties (37), whereas HIV-induced immunosuppression likely plays a clinically significant but reduced role in the etiology of SCCs.

For BCCs, we did not find evidence of an association with immunodeficiency, ART, or other HIV-specific factors. Instead, the increased incidence rate for BCC was observed only for men, particularly MSM. The only additional factors associated with the incidence of BCC in multivariable models were older age and higher Census-based household income. Together, these results suggest that unmeasured confounders possibly related to sex, sexual orientation, and income might have contributed to the higher incidence of BCCs among HIV+ subjects. For example, it is conceivable that sun exposure might differ by sex or sexual orientation, although we did not have data to explore this possibility. Differential screening for BCCs by HIV status is another possible explanation; however, sensitivity analyses that adjusted for number of outpatient visits as a proxy for overall health-care utilization did not substantially alter our findings.

The association between immunodeficiency and SCC in HIV+ subjects suggests that the pathogenesis of cutaneous SCCs may involve an infectious agent, such as a virus, because most cancers linked to immunodeficiency have known viral etiologies (11). In this regard, it is interesting that an association between HPV infection and SCCs has been noted in several recent studies (38–45). Asgari et al. (43) compared HPV DNA prevalence from 85 SCC case subjects and 95 matched control subjects and reported that HPV DNA from β-papillomavirus species 2 was more common in tumors than in tissue adjacent to the SCC lesion or tissue from control subjects. The association of β-papillomavirus species 2 was also reported in a large European case–control study of 689 SCC case subjects and 845 control subjects (44) and in a prospective cohort study in Sweden (42). However, in another case–control study, HPV was detected in only one of 10 tissue specimens from HIV+ individuals with SCCs, and for the single HPV-positive tissue specimen, HPV was also detected in the normal skin control from the same individual (46). Thus, further studies are needed to explore the link between cutaneous SCCs and HPV or other viruses.

There may also be other explanations for the increased incidence of NMSC in HIV+ individuals. For example, some case reports have suggested that certain ART medications may be photosensitizing (47–50), whereas other case reports have suggested HIV infection itself may have photosensitizing effects (51–53). However, additional data are needed to support these mechanisms, including an analysis of individual ART medications.

This study has several limitations. First, there were no data available on key NMSC risk factors, such as skin type, family history, or sun exposure. However, family history of NMSC is not likely to be associated with HIV infection status and, therefore, not likely to be a strong confounding factor. Differences in skin type or sun exposure behaviors by HIV status may have resulted in confounding. However, we restricted the study population to non-Hispanic white subjects to reduce this confounding. Also, the rate ratios for BCC and SCC were of similar magnitude for sun-exposed and non–sun-exposed anatomic locations. Second, other risk factors considered were obtained from routine clinical practice and not in a standardized fashion. Smoking history, for example, was captured during outpatient visit encounters and only routinely in more recent years. The level of detail recorded for risk factors only allowed for broad categorizations (eg, ever or never smoked), and those without documentation of smoking in their medical record were considered unexposed. Third, NMSC diagnoses represented only the first cancer observed during follow-up. Thus, some subjects may have had a prior history of NMSCs. However, we do not believe the lack of information on prior NMSC history undermines our study findings because all NMSC diagnoses for a given subject, including recurrences, likely share similar etiologies (eg, immunodeficiency). Nevertheless, future studies should investigate the association between HIV infection and NMSC recurrence. Fourth, we were unable to completely account for potential screening biases, although adjustment for health-care utilization did not influence results. Finally, study results may have limited generalizability to women, given the smaller sample size, and to those without access to health care. However, this study among insured subjects has the advantage of reduced vulnerability to screening biases compared with studies that include uninsured subjects, albeit here at the cost of reduced generalizability.

The major strength of our study is the inclusion of large, well-characterized populations of HIV+ subjects and matched, demographically similar HIV- subjects from the same health-care system. Another key strength is the near-perfect case ascertainment of HIV infection status and NMSC diagnoses from clinical registries. In addition, information about several key risk factors was obtained from a comprehensive electronic medical record. Finally, the study results are likely to be highly generalizable to those with access to health care because KPNC provides care to approximately 30% of all insured Californians in its most populated areas (54).

In comprehensively evaluating the incidence of NMSCs in HIV+ subjects, we documented a twofold higher incidence rate of BCCs and SCCs, independent of several known risk factors. Immunodeficiency also appeared to be associated with an increased incidence of SCCs but not BCCs. The observed BCC:SCC ratio for HIV+ subjects with CD4 counts of 500 or more cells/μL was similar to that for HIV- subjects (approximately 4:1), whereas for HIV+ subjects with CD4 counts less than 200 cells/μL, there were more SCCs (ie, the BCC:SCC ratio was lower at approximately 2:1). Therefore, routine skin cancer screening is warranted for HIV+ individuals, particularly those with more advanced HIV/AIDS. HIV+ individuals should also be advised to reduce behaviors that may further increase their risk of NMSC, such as excessive sun exposure. Earlier initiation of ART to maintain higher CD4 counts, as emphasized in recent ART guidelines (55), may also help reduce the burden of NMSCs in this population.

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Affiliations of authors: Division of Research, Kaiser Permanente Northern California, Oakland, CA (MJS, WL, EMW, CPQ, MMA); Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD (EAE).