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Epidemiology of non-keratinocytic skin cancers among persons with acquired immunodeficiency syndrome in the U.S.

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Abstract

Objective—Immunosuppression may increase risk for some skin cancers. We evaluated skin cancer epidemiology among persons with acquired immunodeficiency syndrome (AIDS).

Design—We linked data from population-based U.S. AIDS and cancer registries to evaluate risk of non-keratinocytic skin cancers (melanoma, Merkel cell carcinoma, and appendageal carcinomas, including sebaceous carcinoma) in 497,142 persons with AIDS.

Methods—Standardized incidence ratios (SIRs) were calculated to relate skin cancer risk to that in the general population. We used logistic regression to compare risk according to demographic factors, CD4 count, and a geographic index of ultraviolet radiation exposure.

Results—From 60 months before to 60 months after AIDS onset, persons with AIDS had elevated risks of melanoma (SIR=1.3, 95%CI 1.1-1.4, n=292 cases) and, more strongly, of Merkel cell carcinoma (SIR=11, 95%CI 6.3-17, n=17) and sebaceous carcinoma (SIR=8.1, 95%CI 3.2-17, n=7). Risk for appendageal carcinomas increased with progressive time relative to AIDS onset (p-trend=0.03). Risk of these skin cancers was higher in non-Hispanic whites than other racial/ethnic groups, and melanoma risk was highest among men who have sex with men. Melanoma risk was unrelated to CD4 count at AIDS onset (p=0.32). Risks for melanoma and appendageal carcinomas rose with increasing ultraviolet radiation exposure (p-trend<10^{-4} and p-trend=10^{-3}, respectively).

Conclusions—Among persons with AIDS, there is a modest excess risk of melanoma which is not strongly related to immunosuppression and may relate to ultraviolet radiation exposure. In contrast, the greatly increased risks for Merkel cell and sebaceous carcinoma suggest an etiologic role for immunosuppression.

Keywords

AIDS; skin cancer; melanoma; Merkel cell carcinoma; sebaceous carcinoma; appendageal carcinoma; epidemiology

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Author contributions

EL and EAE designed the study and conducted the statistical analyses. GMD, JRT, and JFF contributed expertise regarding skin cancer. All authors contributed expertise regarding epidemiology methods and participated in the interpretation of the data. MMM and EAE provided data for the study. EL and EAE drafted the manuscript, and all authors contributed to critical revision of the manuscript.

Introduction

Persons immunosuppressed due to human immunodeficiency virus (HIV) infection are at increased risk for cancer, most notably for virus-related cancers such as Kaposi sarcoma (KS, due to human herpesvirus 8), non-Hodgkin lymphoma (NHL, due to Epstein Barr virus), and anogenital carcinomas (due to human papillomavirus [HPV]) [1,2]. A similar spectrum of cancer risk is observed among solid organ transplant recipients, who receive immunosuppressive medications to prevent graft rejection [3]. Solid organ transplant recipients also have an elevated risk for both melanoma and, to a greater extent, squamous and basal cell carcinomas (two skin cancers derived from keratinocytes) [3-5], suggesting the role of immunologic mechanisms. Among transplant recipients, squamous cell skin cancers frequently present as highly invasive tumors and are associated with substantial morbidity [6]. Aggressive squamous cell skin cancers have also been described in HIV-infected persons [7,8].

Reasons for the elevated risk of skin cancer in immunosuppressed individuals are not well established. In general, chronic exposure to ultraviolet solar radiation is the major risk factor for various types of skin cancer, which are most common in non-Hispanic whites, who have less protective skin pigment than non-Hispanic blacks and Hispanics [9,10]. Among transplant recipients, exposure to ultraviolet radiation is a risk factor for squamous cell skin cancer [5, 11]. Ultraviolet radiation induces mutations in DNA in normal skin cells and, in addition, may have a local immunosuppressing effect in the skin [12]. Recent studies suggest that some squamous cell skin cancers, especially in transplant recipients, may be caused by HPV [13-15].

Additional rare types of skin cancers have also been described to arise more frequently in transplant recipients and HIV-infected individuals than in the general population. Merkel cell carcinoma, which like melanoma appears to be derived from neural crest progenitor cells, occurs at increased incidence in these populations [16,17]. Of interest, a recent report described detection of a novel polyomavirus in Merkel cell carcinoma tumors [18], suggesting that this cancer may be caused by a virus. In addition, based on several reported case series [4,6,19], transplant recipients appear to be at increased risk for appendageal carcinomas, a group of related tumors showing differentiation toward one or more of the adnexal structures of the skin. Sebaceous carcinoma, a subtype of appendageal carcinoma, often arises on the face, especially the eyelids, and an excess risk has been suggested in transplant recipients and HIV-infected individuals [19-23]. This tumor type also occurs in conjunction with visceral malignancies, especially colon cancer, as part of Muir-Torre syndrome [22,24-27].

In the present study, we utilized linked registry data to quantify the risk of various types of skin cancer in HIV-infected persons with acquired immunodeficiency syndrome (AIDS). Our study examines HIV-related immunosuppression and ultraviolet radiation exposure as factors of potential etiologic importance for these cancers. Cancer registries in the U.S. do not collect information on the occurrence of the two most common types of skin cancer, squamous cell and basal cell skin cancers, so these outcomes could not be included. The present study also does not include the AIDS-defining cancers KS and NHL, which can involve the skin, because these have been thoroughly evaluated in other studies of the HIV/AIDS population. Thus, our study focuses on the occurrence of melanoma, Merkel cell carcinoma, and appendageal carcinomas among persons with AIDS.

Methods

Study population and cancer outcomes

The HIV/AIDS Cancer Match Study links population-based HIV/AIDS and cancer registry databases in nine U.S. states (Connecticut, Florida, Texas, Colorado, Georgia, Massachusetts, Michigan, Illinois and New Jersey) and five metropolitan areas (New York City, Los Angeles, San Diego, San Francisco, and Seattle) [1,2]. Following linkage, registries provided anonymized data to the study investigators at the National Cancer Institute. Institutional review boards approved the study at each registry.

We analyzed cancer risk among people with AIDS during the period spanning from 60 months before to 60 months after AIDS onset (termed “overall cancer risk period”). Through linkage with the cancer registries, data on cancer in this period were available for 505,294 persons diagnosed with AIDS during 1980-2004. We excluded 8,152 with race/ethnicity outside the major categories, leaving 497,142 subjects for this study.

Based on the International Classification of Diseases for Oncology, third edition [28], we studied cancers of the skin (behavior code 3 and topography codes 440-449) of the following subtypes: melanoma (morphology codes 8720-8799), Merkel cell carcinoma (8247), appendageal skin cancers (8110, 8200, 8211, 8390, 8400, 8401, 8403, 8407, 8408, 8409, 8410, 8480, 8940), and, specifically, sebaceous carcinoma (8410). This list includes all major skin cancers listed in the World Health Organization classification [29], except squamous cell carcinoma and basal cell carcinoma (as noted, not captured by cancer registries), and the AIDS-defining malignancies KS and NHL. Merkel cell carcinoma was not reportable to cancer registries before 1986. We excluded from analysis 14 melanomas that occurred at non-skin sites and two Merkel cell carcinomas arising on the lip and within soft tissues of the lower limb; there were no sebaceous carcinomas at non-skin sites. For each patient diagnosed with a skin cancer, for descriptive purposes, we also noted all other cancers recorded by the cancer registry or, for AIDS-defining cancers, by the HIV/AIDS registry.

Statistical analysis

For statistical analyses, only the first occurrence of each skin cancer subtype in each subject was considered. For the overall cancer risk period, we compared cancer risk in people with AIDS to that in the general population using the standardized incidence ratio (SIR). Expected cancer counts were calculated based on rates specific to sex, age, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic), calendar year, and registry. We adjusted expected counts for prevalent cancers (i.e., cancers arising before AIDS onset), to account for mortality following a cancer diagnosis [2]. In addition, we calculated SIRs for specific areas of the skin related to sun exposure [10] and clinical presentation.

As previously [2], we divided the overall cancer risk period into five intervals: 60 to 25 months before AIDS onset, 24 to 7 months before AIDS, 6 months before to 3 months after AIDS onset (AIDS onset period), 4 to 27 months after AIDS onset (early post-AIDS period), and 28 to 60 months after AIDS. To explore the relationship between immunosuppression and cancer risk, we modeled SIRs in these periods as a function of time relative to AIDS onset using Poisson regression [2]. The AIDS period was excluded from this trend test because of possible over-ascertainment of cancers due to clinical evaluations at the time of AIDS onset. We also present SIRs for the period 61 months to 120 months after AIDS onset, but this period is not considered in other calculations because potential losses to follow-up may lead to under-ascertainment of cancer outcomes.

We evaluated other risk factors for these cancers by comparing the proportion of subjects diagnosed with skin cancer during the overall cancer risk period across demographic

subgroups, using the chi-square test and Fisher exact test (when appropriate). We grouped calendar year of AIDS diagnosis into 1980-1989 (little or no antiretroviral treatment available), 1990-1995 (use of single and dual antiretroviral therapy), and 1996-2004 (use of highly active antiretroviral therapy [HAART]). We had information on CD4 count in the AIDS onset period for 308,152 subjects (62%). We used Poisson regression to evaluate the relationship between this CD4 count measurement and cancer risk in the subsequent early post-AIDS period; this analysis could be performed only for melanoma, for which there were sufficient cases.

Finally, to explore the relationship with solar ultraviolet radiation and skin cancer occurrence in the overall cancer risk period, we used geographic estimates of solar ultraviolet radiation exposure published by the National Oceanic and Atmospheric Administration (ftp://ftp.cpc.ncep.noaa.gov/long/uv/cities). We assumed that all patients registered with AIDS in a given area had received the same solar ultraviolet radiation exposure, calculated as the average of published estimates for five calendar years (1996-1998, 2002-2003). For melanoma, there were sufficient cases in the overall cancer risk period for us to evaluate the relationship with ultraviolet exposure across registry areas using logistic regression. We also used logistic regression to model the independent effects on melanoma risk of HIV risk group and ultraviolet radiation exposure.

Results

Characteristics of persons with AIDS are described in Table 1. Eighty percent were male, and the median age at AIDS onset was 38 years. Overall, 38.8% of the cohort were non-Hispanic whites, but this proportion declined over time, and the proportion of non-Hispanic blacks and Hispanics increased. The most common HIV risk group was men who have sex with men (MSM, 43.4%). At AIDS onset, the median CD4 count was 108 cells/mm^3. Half of the subjects lived in U.S. areas with ultraviolet radiation index less than 4.0, while 38.4% lived in areas with an ultraviolet radiation index of at least 5.5.

For the overall cancer risk period, people with AIDS had a 30% increased risk of melanoma (SIR=1.3, 95%CI 1.1-1.4, n=292 cases) (Table 2). Risk was greatly increased for Merkel cell carcinoma (SIR=11, 95%CI 6.3-17, n=17 cases) and, to a lesser extent, for appendageal carcinomas (SIR=4.2, 95%CI 2.5-6.7, n=17 cases). Risk was especially elevated for sebaceous carcinoma (SIR=8.1, 95%CI 3.2-17, n=7 cases), which was the most common subtype of appendageal carcinoma.

As shown in Table 2, the risk for melanoma appeared similarly elevated for tumors of the face/head, trunk, and upper extremities. In contrast, risk was not increased for melanoma of the lower extremities. Risk of Merkel cell carcinoma was significantly increased for all skin sites evaluated. For all appendageal carcinomas (including sebaceous carcinoma), risk was significantly elevated for the face/head, and 3 to 9-fold increased risks (although not significant) were observed at other sites as well. Although risk of sebaceous carcinoma was elevated for the face/head, no sebaceous carcinomas of the eyelid were reported.

Risks for melanoma, Merkel cell carcinoma, and appendageal cancers relative to the time of AIDS onset are depicted in Figure 1. Risk for melanoma increased non-significantly over time (p=0.10, Figure 1A). The trend for Merkel cell carcinoma was not significant (p=0.66, Figure 1B). In contrast, risk of all appendageal carcinomas combined increased significantly over time relative to AIDS onset (p=0.03, Figure 1C). Cases of sebaceous carcinoma were too few to be analyzed separately.

Table 3 compares the risk of these skin cancers across subgroups of the cohort. During the overall cancer risk period, melanoma risk was higher in males than females, while the other tumors were observed only in males. Risk for each cancer type increased with age and was

higher in non-Hispanic whites than in other race/ethnic groups. Melanoma risk was highest among the MSM group, the only HIV risk group with significantly higher risk than the general population (SIR 1.6, 95%CI 1.4-1.8). A similar pattern was seen for appendageal carcinomas (Table 3), with significantly elevated risk observed in MSM (SIR 6.8, 95%CI 3.6-12) and MSM who were also injection drug users (SIR 11, 95%CI 1.3-38). Melanoma risk was consistently elevated across all calendar years of AIDS diagnosis, whereas risk for appendageal carcinomas declined across calendar year of AIDS diagnosis (p-trend=0.03). For melanoma, CD4 counts at AIDS onset were unrelated to incidence in the early post-AIDS period (p-trend=0.32, based on n=185 melanoma cases with data on CD4 counts).

As shown in Table 3, the risk for each cancer appeared to rise with increasing exposure to ultraviolet radiation, as measured by the registry area's ultraviolet index, with significant trends seen for melanoma and appendageal carcinomas. Figure 2 depicts this relationship in more detail for melanoma, restricted to non-Hispanic white adults (among whom the majority of cases occurred). Risk increased with increasing ultraviolet radiation index for melanomas of the face, head, and upper limb (i.e., body sites with the greatest sun exposure, p-trend=0.003, Figure 2A), as well as for melanomas of the trunk, lower limb, and other/unspecified sites (p-trend=0.06, Figure 2B). When we considered all melanoma sites together, risk among non-Hispanic whites was independently associated with HIV risk group (MSM vs. others: odds ratio 1.7, 95%CI 1.2-2.4) and increasing ultraviolet radiation exposure (p-trend=0.005).

Four persons were diagnosed with two melanomas each. Among the melanoma cases, the following additional cancers were seen: 45 with KS, 15 with NHL, and two with Hodgkin lymphoma. Four individuals with Merkel cell carcinoma had additional cancers, including one case each of KS, Hodgkin lymphoma, anal cancer, and carcinoma of unknown type. Among persons with sebaceous carcinoma, one subject also had NHL (subtype unspecified), and one had KS. Finally, among individuals with other appendageal carcinomas, five had additional malignancies: two with KS, one with both KS and NHL (diffuse large B cell subtype), and one each with acute myeloid leukemia and carcinoma of unknown type.

Discussion

Our study is the first to systematically evaluate the epidemiology of skin cancer among HIV-infected persons according to subtype of cancer and in relation to demographic risk factors. Because our study excluded basal and squamous cell carcinomas, the study provides insights only for melanoma and two other rare skin cancer subtypes, Merkel cell carcinoma and appendageal carcinomas. Among almost 500,000 people with AIDS, melanoma was the most common non-keratinocytic skin cancer, but risk was only modestly higher than in the general population. Risk was more strongly elevated for Merkel cell carcinoma and sebaceous carcinoma, a subtype of appendageal carcinoma.

Several of our findings suggest that HIV-induced immunosuppression does not play a major role in the etiology of melanoma in this population. First, the elevation in melanoma risk (SIR 1.3) is small in comparison to risks for other cancers that are linked to immunosuppression (such as KS, with SIRs 3000-50,000, and NHL, with SIRs 20-350) [1,3]. Prior registry-based studies of HIV-infected individuals (two of which used earlier data from our HIV/AIDS Cancer Match Study) and cohort studies likewise described modest SIRs for melanoma (SIRs ranging from 0.2 to 3) [1,2,30-34], and a meta-analysis of prior studies found an overall SIR for melanoma of 1.24 [3]. Melanoma risk is also modestly elevated (2-fold) in solid organ transplant recipients [3]. Second, despite the availability of data on a substantial number of melanoma cases, we did not observe a significant increase in risk with advancing time relative to AIDS onset or lower CD4 count, two indicators of severe immunosuppression. Third, we observed an association between melanoma risk and ultraviolet radiation exposure, as

measured by geographic area of residence (Figure 2), and risk was not elevated for melanomas of the lower extremities (which receive little sun exposure), pointing to an effect of ultraviolet exposure. Fourth, melanoma risk was increased only among MSM with AIDS, the group perhaps most likely to have recreational sun exposure or use tanning beds. Also, MSM are likely to receive frequent skin examinations as part of medical screening for KS lesions, which could increase the detection of early melanoma lesions. Thus, we suggest that the modest excess risk of melanoma among people with AIDS appears to be explained by sun exposure and/or increased medical surveillance. Nonetheless, despite these considerations, it is not possible to exclude that HIV-related immunosuppression incrementally promotes development of melanoma and accounts for the modestly elevated risk observed in people with AIDS.

In contrast, the greatly elevated risk for Merkel cell carcinoma in people with AIDS relative to the general population (SIR 11) points more strongly to an immunologic mechanism. Our results, based on 17 cases, extend our previous report that included only six cases [17]. Although we did not see an increasing risk with AIDS-relative time, the limited number of cases of Merkel cell carcinoma may have reduced our power to detect a trend. It is noteworthy that Merkel cell carcinoma risk is also elevated among immunosuppressed transplant recipients [16]. It seems likely that ultraviolet radiation is a co-factor for Merkel cell carcinoma [35], since these tumors occurred only among non-Hispanic whites in our study.

The increased risk for appendageal carcinomas (SIR 4.2), particularly sebaceous carcinoma (SIR 8.1), resembles the results for Merkel cell carcinoma. We found an increasing risk for appendageal carcinoma with AIDS-relative time (Figure 1C), further implicating immunologic mechanisms. In addition, the decrease over calendar time parallels the availability of increasingly effective HIV therapies that partially restore immunocompetence. Appendageal carcinomas occur more frequently among organ transplant recipients than in the general population [4], and immunosuppression may increase the risk of sebaceous carcinomas in patients with Muir-Torre syndrome [24]. However, none of our subjects with appendageal carcinomas developed colon or other cancers linked to Muir-Torre syndrome. None of our cases of sebaceous carcinoma arose from the eyelid, although tumors of this site have been described in HIV-infected persons and transplant recipients [20-24]. The predominance of appendageal carcinomas among non-Hispanic whites and MSM, and the association with geographic area of residence, suggest that ultraviolet exposure may also contribute to the risk of this tumor [29].

Strengths of our study include its large size and representativeness of the U.S. HIV/AIDS epidemic. Also, the occurrence of cancer was determined through linkage with population-based cancer registries, which provide near-complete ascertainment and detailed information on subtypes of skin cancer. Nonetheless, our study also has several limitations. First, we could not evaluate squamous and basal cell skin carcinomas, because data on these keratinocytic subtypes are not collected by cancer registries. These skin cancers occur frequently in solid organ transplant recipients and manifest an aggressive phenotype [6]. Several case series describe highly invasive squamous cell skin cancers in HIV-infected persons [8,36-38]. In addition, a prior study of HIV-infected military health beneficiaries in the U.S. noted an elevated incidence of squamous and basal cell skin cancers, although the magnitude of risk relative to the general population was not described [39]. Second, even with the large size of our study, the number of cases with Merkel cell carcinoma and sebaceous carcinoma was small, which limited our ability to detect statistical associations. Third, we did not have individual data on important factors that could modify cancer risk, including sun exposure and HAART use. Finally, because we studied persons with AIDS, we were able to evaluate the effect of advanced immunosuppression on skin cancer risk, but it was not possible to fully evaluate risk at an earlier stage of HIV infection. Because CD4 counts were systematically collected only

at AIDS onset, we could not evaluate skin cancer risk in relation to changes in CD4 count over time.

In conclusion, the greatly increased risk of Merkel cell carcinoma and appendageal carcinomas (particularly sebaceous carcinoma) among people with AIDS point to immunosuppression as a major risk factor for these cancers. These observations raise the possibility that these cancers arise, at least in part, from loss of immune control of oncogenic viruses. The recent discovery of a novel polyomavirus in Merkel cell carcinoma tumors is consistent with this hypothesis [18], and some investigators have detected HPV in sebaceous carcinomas [40-42]. Further research is needed to characterize the role of these viruses, or as yet undiscovered agents, in the etiology of these skin cancers. Finally, the modestly elevated risk of a common skin cancer (melanoma) and the greatly elevated risk of two rare non-keratinocytic skin cancers (as well as reports of aggressive squamous cell skin cancers in HIV-infected persons) suggest a need for guidelines aimed at prevention and early detection of skin cancers in HIV-infected individuals.

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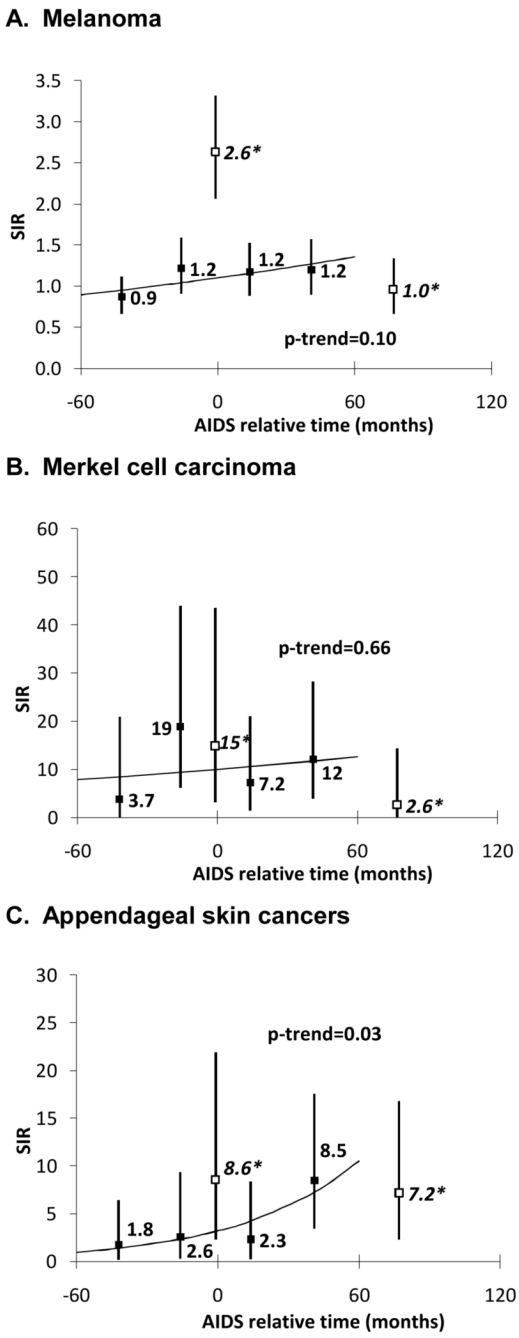
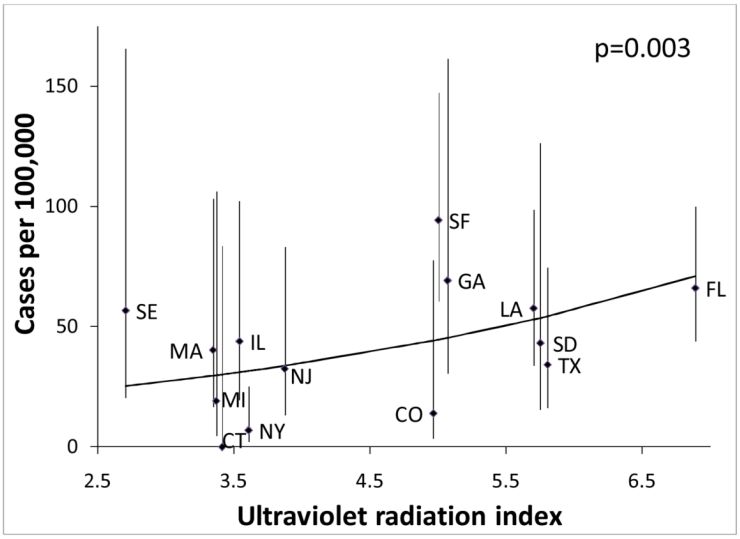


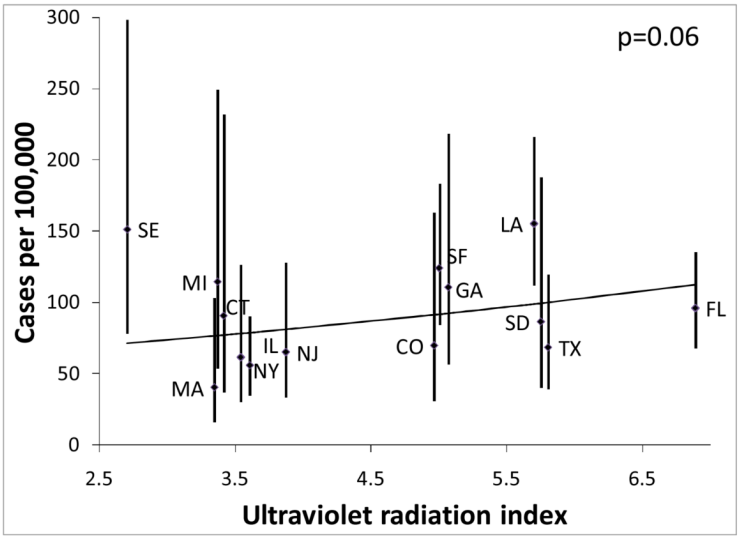
Figure 1.

Risk of skin cancers among persons with AIDS, as a function of time relative to AIDS onset. Results are shown for melanoma (panel A), Merkel cell carcinoma (panel B), and all appendageal skin carcinomas (panel C). The standardized incidence ratios are shown as squares, with surrounding 95% confidence intervals as vertical lines. The curved line corresponds to the trend estimated in Poisson regression. The p-value for the trend test is also indicated. Note that the vertical axis differs across the panels. The time periods used in the trend test are shown with a solid square, while the time periods excluded from the trend test are shown with an open square. The two excluded periods are from 6 months before to 3 months after AIDS onset, because of possible over-ascertainment of cancers due to clinical evaluations

associated with diagnosis of AIDS, and from 61 months to 120 months after AIDS onset, because potential losses to follow-up may lead to under-ascertainment of cancer outcomes.



Panel A. Melanoma of the face, head, and upper limb.



Panel B. Melan

Figure 2.

Melanoma risk among persons with AIDS, according to ultraviolet radiation exposure. Results are shown for melanomas of the face, head, and upper limb (Panel A) and melanomas of the trunk, lower limb, and other/unspecified sites (Panel B). Results are restricted to non-Hispanic white adults (age 15 years or older at AIDS onset) and are expressed as the number of melanoma cases per 100,000 subjects during the overall cancer risk period (60 months before to 60 months after AIDS onset). The analysis includes 88 melanoma cases of the face, head, and upper limb, and 176 cases of the trunk, lower limb, and other/unspecified sites. The trend line and associated p-value were derived using logistic regression. Note that the vertical axis differs across the panels.

Table 1

Characteristics of subjects (N=497,142) in the U.S. HIV/AIDS Cancer Match Study, according to calendar year of AIDS diagnosis

		All		Year of AIDS diagnosis					
				1980-1989		1990-1995		1996-2004	
		N	%	N	%	N	%	N	%
Overall		497,142	100.0	86,518	100.0	228,523	100.0	182,101	100.0
Sex									
	Male	399,064	80.3	76,394	88.3	186,352	81.5	136,318	74.9
	Female	98,078	19.7	10,124	11.7	42,171	18.5	45,783	25.1
Age at AIDS onset, years									
	0-14	6,094	1.2	1,711	2.0	3,185	1.4	1,198	0.7
	15-29	76,368	15.4	16,504	19.1	36,386	15.9	23,478	12.9
	30-39	216,265	43.5	40,368	46.7	102,616	44.9	73,281	40.2
	40-49	138,701	27.9	19,243	22.2	61,827	27.1	57,631	31.6
	50+	59,714	12.0	8,692	10.0	24,509	10.7	26,513	14.6
Race/ethnicity									
Non-Hispanic white		192,690	38.8	44,949	52.0	93,424	40.9	54,317	29.8
Non-Hispanic black		202,874	40.8	26,826	31.0	87,641	38.4	88,407	48.5
	Hispanic	101,578	20.4	14,743	17.0	47,458	20.8	39,377	21.6
Mode of HIV exposure									
	MSM	215,599	43.4	49,025	56.7	102,639	44.9	63,935	35.1
	IDU	125,971	25.3	21,272	24.6	66,724	29.2	37,975	20.9
MSM and IDU		27,497	5.5	5,855	6.8	13,486	5.9	8,156	4.5
Heterosexual		60,761	12.2	3,430	3.9	23,821	10.4	33,510	18.4
Other/unspecified		67,314	13.5	6,936	8.0	21,853	9.6	38,525	21.2
CD4 cell count at AIDS onset, cells/μL									
	Missing	188,990	38.0	81,670	94.4	82,954	36.3	24,366	13.4
	0-49	96,439	19.4	1,031	1.2	46,979	20.6	48,429	26.6
	50-99	49,585	10.0	730	0.8	23,960	10.5	24,895	13.7
	100-149	49,836	10.0	804	0.9	23,235	10.2	25,797	14.2
	150-199	67,723	13.6	1,191	1.4	31,587	13.8	34,945	19.2
	200+	44,569	9.0	1,092	1.3	19,808	8.7	23,669	13.0

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		All		Year of AIDS diagnosis					
				1980-1989		1990-1995		1996-2004	
		N	%	N	%	N	%	N	%
Ultraviolet radiation index									
	Less than 4.0	248,404	50.0	48,265	55.8	118,322	51.8	81,817	44.9
	4.0-5.4	57,964	11.7	13,350	15.4	26,774	11.7	17,840	9.8
	5.5+	190,774	38.4	24,903	28.8	83,427	36.5	82,444	45.3

Abbreviations: AIDS acquired immunodeficiency syndrome; HIV human immunodeficiency virus; IDU intravenous drug user; MSM men who have sex with men

Table 2

Risk of skin cancers among subjects in the HIV/AIDS Cancer Match Study

Skin cancer subtype, location	Observed cases	SIR	(95%CI)
Melanoma	292	1.3	(1.1-1.4)
Face/head	40	1.2	(0.8-1.6)
Trunk	133	1.4	(1.1-1.6)
Upper extremities	56	1.2	(0.9-1.6)
Lower extremities	28	0.8	(0.5-1.2)
Other/unspecified	35	2.3	(1.6-3.1)
Merkel cell carcinoma	17	11	(6.3-17)
Face/head	6	13	(4.8-29)
Trunk	3	9.3	(1.9-27)
Extremities	5	8.2	(2.7-19)
Other/unspecified	3	17	(3.5-49)
All appendageal carcinomas*	17	4.2	(2.5-6.7)
Face/head	10	4.5	(2.2-8.6)
Trunk	3	3.3	(0.7-9.5)
Extremities	3	3.7	(0.8-11)
Other/unspecified	1	9.0	(0.2-50)
Sebaceous carcinoma	7	8.1	(3.2-17)
Face/head	3	5.0	(1.0-15)
Trunk	0	0.0	(0.0-21)
Extremities	3	45	(9.2-131)
Other/unspecified	1	33	(0.8-184)

Abbreviations: CI confidence interval; SIR standardized incidence ratio

*Appendageal carcinomas include 7 sebaceous carcinomas, 5 appendageal skin cancers not otherwise specified, 3 sweat gland adenocarcinomas, 1 adenoid cystic carcinoma, and 1 apocrine adenocarcinoma.

Table 3

Risk of skin cancers among subjects in the HIV/AIDS Cancer Match Study, according to demographic characteristics

		Subjects	Melanoma			Merkel cell carcinoma			All appendageal carcinomas			Sebaceous carcinoma		
			N	Cases/10^5	p*	N	Cases/10^5	p*	N	Cases/10^5	p*	N	Cases/10^5	p*
Overall		497,142	292	58.7		17	3.4		17	3.4		7	1.4	
Sex					$<10^{-4}$			0.04			0.03			0.36
	Male	399,064	276	69.2		17	4.3		17	4.3		7	1.8	
	Female	98,078	16	16.3		0	0.0		0	0.0		0	0.0	
Age at AIDS onset, years					$<10^{-4}$			$<10^{-4}$			5×10^{-4}			7×10^{-3}
	0-14	6,094	0	0.0		0	0.0		0	0.0		0	0.0	
	15-29	76,368	17	22.3		0	0.0		0	0.0		0	0.0	
	30-39	216,265	84	38.8		2	0.9		5	2.3		2	0.9	
	40-49	138,701	119	85.8		7	5.0		5	3.6		1	0.7	
	50+	59,714	72	120.6		8	13.4		7	11.7		4	6.7	
Race/ethnicity					$<10^{-4}$			10^{-4}			6×10^{-3}			0.61
Non-Hispanic white		192,690	261	135.5		15	7.8		13	6.7		4	2.1	
Non-Hispanic black		202,874	8	3.9		0	0.0		3	1.5		2	1.0	
Hispanic		101,578	23	22.6		2	2.0		1	1.0		1	1.0	
Mode of HIV exposure					$<10^{-4}$			0.21			0.03			0.29
MSM		215,599	226	104.8		12	5.6		13	6.0		5	2.3	
IDU		125,971	19	15.1		2	1.6		1	0.8		0	0.0	
MSM and IDU		27,497	10	36.4		0	0.0		2	7.3		1	3.6	
Heterosexual		60,761	14	23.0		2	3.3		1	1.6		1	1.6	
Other/unspecified		67,314	23	34.2		1	1.5		0	0.0		0	0.0	
Year of AIDS diagnosis					0.32			-†			0.03			0.21
1980-1989		86,518	57	65.9		0	0.0		5	5.8		2	2.3	
1990-1995		228,523	134	58.6		12	5.3		10	4.4		4	1.8	
1996-2004		182,101	101	55.5		5	2.7		2	1.1		1	0.5	
Ultraviolet radiation index					10^{-4}			0.30			4×10^{-3}			0.46
Less than 4.0		248,404	85	34.2		6	2.4		2	0.8		2	0.8	
4.0-5.4		57,964	66	113.9		3	5.2		4	6.9		2	3.5	
5.5+		190,774	141	73.9		8	4.2		11	5.8		3	1.6	

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Abbreviations: AIDS acquired immunodeficiency syndrome; HIV human immunodeficiency virus; IDU intravenous drug user; MSM men who have sex with men

[*] P-values for sex, race, mode of HIV exposure, region and ultraviolet radiation index were tests of heterogeneity, while p-values age and year of AIDS diagnosis were tests of trend.

[†] The trend over calendar time could not be evaluated reliably for Merkel cell carcinoma because this cancer was not systematically ascertained before 1986.