Risk of skin cancer in patients with HIV

a Danish nationwide cohort study

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Title

Risk of skin cancer in HIV-infected patients: a Danish nationwide cohort study

Authors

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ABSTRACT

Background:

The risk of skin cancer in HIV-infected patients has not been extensively studied.

Objective:

To determine the risk of skin cancer in HIV-infected patients and compare it with the risk in the background population.

Methods:

In a matched, nationwide population-based cohort study we compared the risk of skin cancer in 4280 HIV-infected patients from the Danish HIV cohort study with a background population cohort, according to the level of immunosuppression and route of transmission.

Primary outcomes were time to first basal cell carcinoma (BCC), squamous cell carcinoma (SCC), or malignant melanoma (MM).

Results:

HIV-infected patients had an increased risk of BCC and SCC with IRRs of 1.79 (95% CI 1.43 – 2.22) and 5.40 (95% CI 3.07 – 9.52), respectively, compared with the background population. We observed no increased risk of MM. Low nadir CD4 cell count was associated with an increased risk of SCC. The increased risk of BCC among HIV-infected patients was restricted to men who had sex with men.

Limitations:

Observational design. Small number of patients with melanoma.

Conclusion:

HIV-infected patients have an increased risk of BCC and SCC.. Low nadir, but not current, CD4 cell count as a marker of immunosuppression was associated with an increased risk of SCC.

Key words:

Skin cancer

HIV-infection

Basal cell carcinoma

Squamous cell carcinoma

Malignant melanoma

Cohort study

Capsule Summary:

• The risk of skin cancer may be increased in HIV-infected patients.

• HIV-infected patients have an increased risk of BCC and SCC. Route of infection is associated with BCC while nadir but not current CD4 cell count is associated with SCC.

• Physicians should be aware of the increased risk of BCC and SCC in HIV-infected patients.

Background

Skin cancer risk is increased in immunocompromised individuals. [1,2] After the introduction of highly active antiretroviral therapy (HAART) the overall life expectancy for well-treated HIV-infected patients is approaching that of the background population.[3] The immunological recovery resulting from HAART has lowered the incidence of AIDS defining cancers while there is a persistently increased risk of some non-AIDS defining cancers.[4] Whether HIV-infected patients are at increased risk of skin cancer is not well documented partially since few countries provide reliable information on keratinocyte skin cancers (KSC), in particular basal cell carcinoma (BCC). A two-fold increased risk of BCC and squamous cell carcinoma (SCC) was demonstrated in a study of HIV-infected patients living in the US. [5]

In this study, we aim to estimate the risk of non-AIDS defining skin cancer, both KSC (comprising BCC and SCC) and MM in HIV-infected patients compared with a sex- and age matched cohort from the background population as well as siblings of these two cohorts. This unique study design using high quality population-based, nationwide data enabled us to address potential confounding by skin type and family related sun behaviour and to provide data on skin cancer risk in HIV-infected patients from more northern parts of the world.

Methods

The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). We used four national registries as data sources following approval from the Danish Data Protection Agency. According to Danish law, no human participant committee approval is required for register-based studies.

Setting:

The Danish population consists of 5.7 million inhabitants [6] with an estimated adult HIV prevalence of 0.1%. HIV-infected patients are treated in eight specialized HIV centers, and followed on outpatient basis every 12–24 weeks. Antiretroviral treatment is provided free of charge to all HIV-infected residents of Denmark.

Data sources:

We used the unique 10-digit civil registration number assigned to all individuals in Denmark [7] to link the data sources described below.

The Danish HIV cohort study (DHCS)

The DHCS is a prospective, nationwide, population-based cohort study of all HIV-infected patients aged 16 years or older at time of diagnosis, treated at Danish HIV centers from 1 January 1995 with consecutive ongoing enrolment. [8] A detailed description of the cohort has previously been published. [9] Yearly updates are performed and date of first positive HIV-test and start of antiretroviral treatment (HAART) are important cohort parameters as well as route of infection, CD4 cell counts and HIV RNA measurements.

The Danish Civil Registration System (DCRS)

The DCRS established in 1968 stores information of vital status and demographic data on all Danish citizens. [7] We collected date of birth, sex, loss to follow-up and death from this register.

The Danish Cancer register (DCR)

The DCR was established in 1943 and records cancer diagnoses. Cancers are classified according to modified ICD-7 diagnoses from 1943 to 1977 and ICD-10 from 1978 and up. Hospital departments (including pathology), and general practitioners report to the DCR upon first diagnosis of cancer and on change of initial cancer diagnosis. Reporting is mandatory, and the proportion of morphologically verified tumors is 89%. [10] From this register, we collected data on skin cancer diagnosis.

Study population/inclusion and exclusion criteria

All HIV-infected patients of Danish origin from the DHCS aged 16 years or more at time of diagnosis were included. For every HIV patient we randomly selected five age-and sex-matched individuals of Danish origin from the background population (“the matched background cohort”) being alive and living in Denmark at the date of inclusion. Danish origin was defined as one or both parents being born in Denmark and having Danish citizenship. This restriction by country of origin was applied to reduce potential bias by differences in skin type between HIV-infected patients and the matched background population. Date of inclusion was defined as 1 January 1995, or first date of HIV diagnosis which ever came last. We excluded patients with skin cancer prior to study enrolment.

For both HIV-infected patients and the matched background cohort we included siblings in two sibling cohorts. In the DCRS, parents’ civil registration number is included for more than 99% of persons born after 1952, less in persons born before. [11] We included siblings if they had at least one common parent, were alive and living in Denmark at time of study inclusion.

Outcome

The primary study outcome was time to first BCC, SCC or MM. We identified the skin cancers by the use of the ICD-10 diagnoses C43.0-C439 (MM) and C44.0-C44.9 (BCC and SCC) coupled with the following morphology codes; M80902, M80903, M80923, M80933 (BCC) and M80703, M80713, M80743, M80753, M80763 (SCC). SCCs and MM in other locations than the skin were not included.

Statistical analysis

Person-years at risk (PYR) were calculated as time from study inclusion to the date of first cutaneous cancer, death, loss to follow-up, emigration or 31 December 2014, whichever came first. Incidence rates (IR) with corresponding 95% confidence intervals (CI) were calculated for BCC, SCC and MM. By subtraction, differences in each outcome between the patient and background cohorts were calculated with corresponding 95% CI. Incidence rate ratios (IRRs) of skin cancer for HIV-infected patients compared with the matched background cohort were estimated using Poisson regression models. To address potential association with immunosuppression, we fitted a Poisson regression model for HIV-infected patients only where the following variables were considered: current CD4 cell count below 350 cells/µL (time updated variable), ever exposed to HAART (time updated variable), nadir CD4 cell count before study inclusion, sex, and age. As few patients were diagnosed with skin cancer before first treatment with HAART, in the final analysis, we only included HIV-infected patients exposed to HAART. Therefore, we were unable to address the impact of HAART. Consequently, in the final model, IRRs were estimated for current CD4 cell count (<350 versus >= 350 cells/µL), nadir CD4 cell count (per cell/µL increase), sex and age (per year increase).

In order to investigate potential confounding from family related factors, in particular the level of sun exposure during childhood and skin type, we compared the risk of skin cancer between siblings of HIV-infected and siblings of the matched background cohort. Further, all analyses were stratified by route of infection (men who have sex with men (MSM) versus other routes of infection), as it has been suggested that HIV-infected MSM have an increased recreational sun exposure. [12] The cumulative incidence function was used to estimate the absolute risk of KSC, with death handled as competing risk.[13]

Results

Of the 6323 HIV-infected patients in the DHCS, we excluded 2043 (32.3%), the majority excluded due to other origin than Danish (Supplementary Figure 1). This left 4280 HIV-infected patients, who were followed for more than 41,000 PYRs. We identified 21,399 individuals for the matched background cohort, followed for more than 274,000 PYRs (Supplementary Figure 1). For descriptive data, see Table 1.

Risk of BCC

The IR of BCC was 2.43 (95% CI: 2.00 – 2.95)/1000 PYR) in HIV-infected patient and 1.43 (95% CI: 1.30 – 1.58) /1000 PYR in the matched background cohort with a difference of 1.00 (95% CI: 0.50 – 1.49)/1000 PYR (Table 2).

Figure 1 illustrates the cumulative incidence of BCC. The risk of a BCC diagnosis was increased for the HIV-infected patients (IRR 1.79 (95% CI: 1.43 – 2.22)). Siblings of HIV-infected patients did not have an increased risk of BCC compared with siblings of the matched background cohort (IRR: 1.02 (95% CI: 0.75 – 1.40)).

Neither current nor nadir CD4 cell count were associated with risk of BCC (Table 3).

The risk of BCC differed according to route of infection. Those, who reported MSM as the route of HIV-transmission had an increased risk of BCC with IRR of 2.30 (95% CI: 1.76-3.02) compared with the matched background cohort. For other routes of HIV-infection, no increased risk of BCC was observed (Table 2).

Risk of SCC

The IR of SCC was 0.50 (95% CI: 0.32 – 0.77)/1000 PYR) in HIV-infected patient and 0.10 (95% CI: 0.07 – 0.15)/1000 PYR in the matched background cohort with a difference of 0.40 (95% CI: 0.18 – 0.62)/1000 PYR (Table 2).

Figure 2 illustrates the cumulative incidence of SCC. The risk of being diagnosed with SCC was increased among HIV-infected patients compared with the matched background cohort with an IRR of 5.40 (95% CI:

3.07 – 9.52) (Table 2). We did not detect any difference in risk of SCC when comparing siblings of HIV-infected patients with siblings of the matched background cohort (IRR: 0.70 (95% CI: 0.09 – 5.66)). Nadir, but not current CD4 cell count was associated with a decreased risk of SCC (Table 3). The increased risk of SCC was observed in both MSM as well as HIV patients reporting heterosexual route of HIV transmission (Table 2).

Risk of MM

The risk of developing MM seemed not to be increased among HIV-infected patients (IRR of 0.60 (95% CI: 0.28 – 1.31)) or their siblings (IRR of 0.95 (95% CI: 0.55 – 1.61)) when compared with the matched background cohort and siblings of the matched background cohort, respectively. Since all diagnoses of MM among HIV-infected patients appeared when the CD4 cell count was <350 cells/µL no further investigation of the impact of immunosuppression was done.

Discussion

In this nationwide, population-based cohort study we observed a two-fold increased risk of BCC and a five-fold increased risk of SCC in HIV-infected patients compared with the background population. The increased risk of BCC was restricted to patients reporting MSM as route of HIV-infection. There seemed to be an association between immunosuppression and SCC-risk for HIV-infected patients. The risk of MM was not increased when compared with the background population but low number of MM cases makes definitive conclusion difficult.

One of the main risk factors for developing skin cancer is UV-exposure. In our study, we assumed that skin type and level of sun exposure in childhood were comparable between siblings. We found no increase in BCC-, SCC- or MM-risk among siblings of HIV-infected patients compared with siblings of the matched background cohort; hence, the data did not support confounding by sun exposure in early childhood as an explanation of the increased risk of BCC and SCC among HIV-infected patients.

However, since use of sunbeds mostly happens in youth/adulthood, this might differ between siblings. Therefore, an increased risk of KSC in HIV-infected patients, but not their siblings, could be a result of either the immunosuppression caused by the HIV-infection or sunbed use in youth/adulthood. The increased risk of BCC was only seen in patients reporting MSM as route of infection. One could argue that the increased risk of BCC might be driven primarily by sun exposure in youth/adulthood not accounted for by the sibling-model since previous data suggests that HIV-infected MSM might have an increased recreational UV-exposure.[12] Further, no association between BCC and immunosuppression was observed. Difference in lifestyle habits including traveling as well as occupation might also influence the risk; however, data on these parameters were not available for this study.

For SCC the picture was somewhat the opposite. SCC seemed to be associated with more severe immunosuppression as reflected by lower nadir CD4 cell count. Further, the increased SCC risk was not restricted to any route of infection. This corresponds to data from other studies in HIV-infected individuals and in solid organ transplant recipients, where the incidence of SCC has been reported to be proportional to the level of immunosuppression. [5,14,15] Our results were somehow contradictory in terms of CD4 cell count with nadir, but not current CD4 cell count being associated with risk of SCC. We cannot conclude meaningfully on current CD4 cell count due to very wide CI, but it could be hypothesized that nadir CD4 count is indicative of immunosuppressive history and represents a time lag between immunosuppression and skin cancer while this exposure lag is not seen with current CD4 cell counts.

Human papillomavirus (HPV) alpha is associated with cervical, anogenital-and oropharyngeal cancers. HPV beta has been detected in a proportion of cutaneous SCC, and a possible etiological role has been suggested, especially in the immunosuppressed individuals. However, no mechanism of carcinogenesis has yet been found. [16,17]

A study from California found a 2.6 fold increased risk of SCC and a 2.1-increased risk of BCC when comparing HIV-positive with HIV-negative patients.[5] The risk of BCC was almost comparable to our results, while the risk of SCC was substantially higher in our study. Numerous factors could affect rates of SCC among both HIV-infected patients and their HIV negative counterparts, which in turn will affect the estimated relative risk of SCC comparing these two groups. In the study from California, SCCs in situ were included. Further, the Californian cohort was older and had a higher CD4 cell count - the latter probably contributes substantially to the lower risk of SCC observed in the American study. Unknown and residual confounding as well as unrecognized interaction between HIV and confounders might also affect the associations found. Finally, differences in sun exposure and skin type between California and Denmark might influence the results though one would expect this to apply for both HIV-infected and controls.

Our study was not designed to address the potential effect of skin cancer prevention in HIV-infected patients. In a hypothetical scenario in which prevention reduced the incidence of KSC to that of the background population, the cohort of HIV-infected patients would have to be observed for approximately 1000 PYRs to avoid one case of BCC and 2500 PYRs to avoid one case of SCC.

Major strengths of our study are the nationwide, population-based design with long follow-up, and the high quality and almost complete coverage of Danish registries. Furthermore, potential confounding from family related factors such as skin type and sun exposure in childhood is addressed by comparing siblings. Finally, we matched HIV-infected patients and the matched background cohort on country of origin (Denmark) reducing the potential bias introduced by differences in skin type between the two cohorts.

A limitation to our study is reliance on register-based diagnoses without additional validation. A comprehensive assessment has demonstrated that the completeness and validity of the DCR is very high (95-98%). [18] Although including more than 4000 HIV-infected patients with long-term follow-up, we only observed small numbers of SCC and MM, limiting the power of our study and hindering more elaborate stratification. Finally, surveillance bias due to frequent consultations among HIV-infected patients might contribute to the association between KSC and HIV. However, a short-term (positive) association due to diagnostic bias alone would be followed by a later compensatory negative association (e.g., a KSC risk below one during extended follow-up), which was not found. Therefore, we do not believe that diagnostic bias alone explains our findings.

Conclusion

With this nation-wide, population-based cohort study, we have demonstrated that HIV-infected patients have an increased risk of BCC and SCC. Due to few events of MM solid conclusion cannot be made regarding risk of MM in HIV-infected individuals. The risk of SCC seemed to increase with increasing level of immunosuppression while the increased risk of BCC was restricted to patients reporting MSM as route of infection.

Abbreviations:

HAART: Highly active antiretroviral therapy

KSC: Keratinocyte skin cancer

BCC: Basal cell carcinoma

SCC: Squamous cell carcinoma

MM: Malignant melanoma

DHCS: The Danish HIV cohort study

DCRS: The Danish Civil Registration System

DCR: The Danish Cancer register

PYR: Person-years at risk

IR: Incidence rate

CI: Confidence interval

IRR: Incidence rate ratios

MSM: Men who have sex with men

HPV: Human papillomavirus

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Figure legends

Figure 1: The cumulative incidence of basal cell carcinoma (BCC) among HIV-infected patients compared with the matched background population.

F**igure 2**: The cumulative incidence of squamous cell carcinoma (SCC) among HIV-infected patients compared with the matched background population.

Table 1. Baseline characteristics of HIV-infected patients and the matched background population.

	HIV-infected patients, n= 4280	**Age- and sex matched background cohort, n= 21.399**	**Siblings of HIV-infected patients, n = 5647**	**Siblings of the background cohort, n = 26.875**
Males, n (%)	3641 (85.1)	18.204 (85.1)	3020 (53.5)	14.137 (52.5)
Age at study inclusion, median (IQR)	38.6 (31.7-46.8)	38.6 (31.7-46.8)	34.2 (29.3 – 39.7)	34.5 (29.7 – 39.7)
Route of infection, n (%)				
MSM	2327 (54.4)	n.a.	n.a.	n.a.
Heterosexually	1216 (28.4)	n.a.	n.a.	n.a.
Intravenous drug use	502 (11.7)	n.a.	n.a.	n.a.
Other	235 (5.5)	n.a.	n.a.	n.a.
CD4 cell count at study inclusion (cells/µL), median (IQR)	300 (120-504)	n.a.	n.a.	n.a.

Abbreviations: MSM: men who have sex with men, IQR: interquartile range

Table 2. Risk of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) among HIV-infected patients of Danish origin compared with the matched background population.

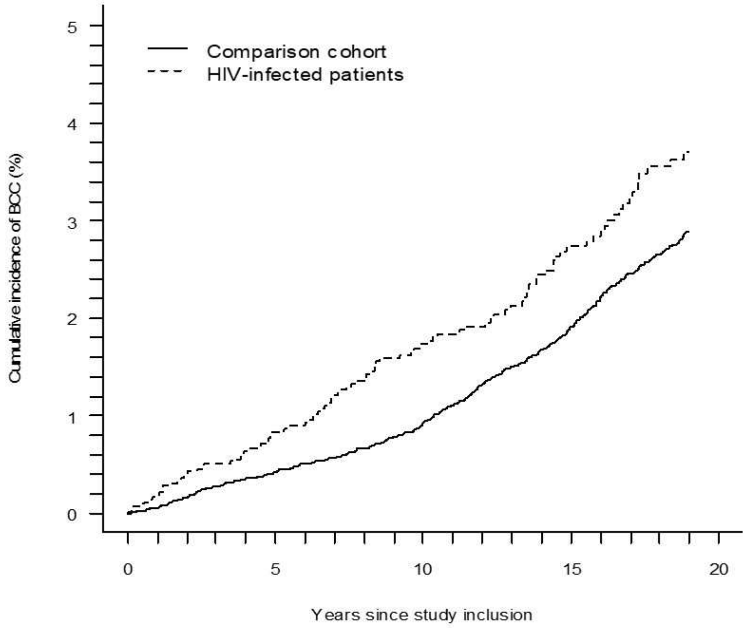
		BCC			SCC			MM		
Route of infection		*n*	Rate per 1000 PYR (95% CI)	IRR (95% CI) *	*n*	Rate per 1000 PYR (95% CI)	IRR (95% CI) *	*n*	Rate per 1000 PYR (95% CI)	IRR (95% CI) *
All	HIV-infected patients	101	2.43 (2.00 – 2.95)	1.79 (1.44 – 2.22)	21	0.50 (0.32 – 0.77)	5.40 (3.07 – 9.52)	7	0.17 (0.08 – 0.35)	0.60 (0.28 – 1.31)
	Matched background cohort	392	1.43 (1.30 - 1.58)	Ref.	28	0.10 (0.07 - 0.15)	Ref.	79	0.29 (0.23 – 0.36)	Ref.
MSM	HIV-infected patients	70	3.06 (2.42 – 3.87)	2.30 (1.76 – 3.02)	12	0.52 (0.30 – 0.92)	4.30 (2.10 – 8.82)	4	0.17 (0.07 – 0.47)	0.60 (0.21 – 1.66)
	Matched background cohort	208	1.42 (1.24 – 1.62)	Ref.	20	0.14 (0.09 – 0.21)	Ref.	45	0.31 (0.23 – 0.41)	Ref.
Other	HIV-infected patients	31	1.66 (1.17 – 2.36)	1.18 (0.81 – 1.73)	9	0.48 (0.25 – 0.93)	8.09 (3.12 – 21.00)	3	0.16 (0.05 – 0.50)	0.61 (0.19 – 1.98)
	Matched background cohort	184	1.44 (1.25 – 1.67)	Ref.	8	0.06 (0.03 – 0.13)	Ref.	34	0.27 (0.19 – 0.37)	Ref.

* adjusted for age and sex. Abbreviations: BCC: Basal cell carcinoma, PYR: person years of observation, IRR: incidence rate ratio, CI: confidence interval, SCC: squamous cell carcinoma, MSM: men who have sex with men

Table 3. Risk of BCC and SCC among HIV-infected patients of Danish origin according to current CD4 cell count, nadir CD4 cell count, sex and age.

	IRR (95% CI) for BCC	IRR (95% CI) for SCC
CD4 cell count <350	0.55 (0.28-1.07)	1.12 (0.36-3.46)
CD4nadir (per cell/µL increase)	0.999 (0.998-1.009)	0.994 (0.990-0.999)
Sex	2.12 (0.77-5.87)	2.04 (0.27-15.68)
Age (per year increase)	1.07 (1.05-1.10)	1.12 (1.07-1.18)

Abbreviations: IRR: incidence rate ratio, CI: confidence interval


Comparison cohort
HIV-infected patients
Cumulative incidence of BCC (%)
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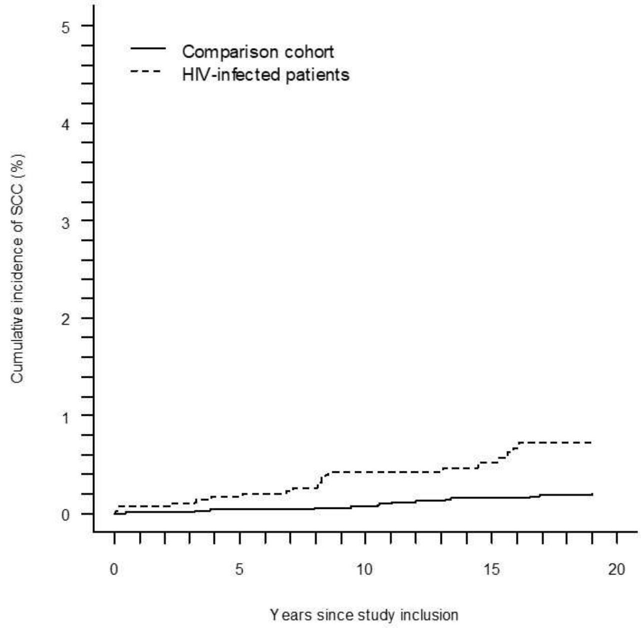
1
2
3
4
5
0
5
10
15
20
Years since study inclusion


Comparison cohort
HIV-infected patients
Cumulative incidence of SCC (%)
0
1
2
3
4
5
0
5
10
15
20
Years since study inclusion