Risk factors for anal cancer in persons infected with HIV: a nested case-control study in the Swiss HIV Cohort Study

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Abstract (word count: 250)

**Background** Although persons infected with HIV (PHIV), particularly men having sex with men (MSM), are at excess risk for anal cancer, it has been difficult to disentangle the influences of anal exposure to human papillomavirus (HPV) infection, immunodeficiency and combined antiretroviral therapy (cART). **Methods** A case–control study was nested in the Swiss HIV Cohort Study (SHCS). Fifty nine anal cancers identified in the SHCS or through linkage with Swiss Cancer Registries (1992-2011) were individually matched to 259 controls. For a sub-set of 41 cases and 114 controls, HPV antibodies were tested from serum samples using a multiplex Luminex-based assay. Odds ratios were estimated by conditional logistic regression. **Results** A majority of anal cancer cases were MSM (72.9%) and diagnosed in the cART era (98.3%). Current smoking was significantly associated with anal cancer (OR=2.59, 95% CI:1.25-5.34), as were antibodies against L1 (OR=4.52, 95% CI:2.00-10.2) and E6 (OR=∞) of HPV16. Anal cancer was significantly associated with low CD4+ cell counts, whether measured as nadir (OR per 100μL decrease = 1.53, 95% CI 1.18-2.00), or at cancer diagnosis (OR per 100μL decrease = 1.24, 95% CI:1.08-1.42). However, strongest influence of CD4+ cell count was at 6-7 years prior to anal cancer (OR per 100μL decrease = 1.58, 95% CI:1.27-1.97), and already at moderate levels of immunosuppression (OR for 200-499 versus 500 cells/μL=4.42, 95% CI:1.19-16.4). Associations with cART were not statistically significant. **Discussion** Smoking cessation and avoidance of even moderate levels of immunosuppression among PHIV appear important to avoid long-term anal cancer risks.

**Background**

In the Swiss HIV Cohort Study (SHCS) [Franceschi et al., 2010], as in other studies of persons infected with HIV (PHIV) [Grulich et al., 2007], there is a 30-fold excess of anal cancer in comparison to the general population. Anal cancer incidence is particularly high among, but not limited to, men having sex with men (MSM) [Clifford et al., 2005], for whom estimates exceed 100/100,000 person years in the era of combined antiretroviral therapy (cART) [Machalek et al., 2012;Silverberg et al., 2012].

Anal cancer is a consequence of infection with high-risk human papillomavirus (HPV) types, mainly HPV16 (ref IARC monograph 100B). However, in addition to increased sexual exposure to anal HPV infection, excess risk in PHIV likely reflects the influence of immunodeficiency on HPV natural history. Immunodeficiency has been linked to increased anal cancer risk using the measures of nadir CD4+ count [Patel et al., 2008;Piketty et al., 2008;Crum-Cianflone et al., 2010;D'Souza et al., 2008;Powles et al., 2009], current CD4+ count [Reekie et al., 2010], baseline CD4+ count [Silverberg et al., 2012], or duration of CD4+ cell counts below 200/µl [Kesselring et al., 2011;Guiguet et al., 2009]. However, it is still not well understood when in the long evolution from HPV infection to anal cancer development that the influence of immunodeficiency is most important.

The effects of cART-related improvements in immunity on anal cancer risk also remain unclear. Whilst some cohort studies of PHIV have reported strong increases in anal cancer incidence since the introduction of cART [Shiels et al., 2011;Patel et al., 2008;Piketty et al., 2008;Franceschi et al., 2010], others have not [Powles et al., 2009;van Leeuwen et al., 2009], and historical trends are additionally complicated by vast increases in the life expectancy of PHIV in the cART era [Franceschi et al., 2010].

Thus, we undertook a case–control study nested within the Swiss HIV Cohort Study (SHCS), specifically designed to characterize the influence of immunodeficiency and cART on the development of anal cancer among PHIV.

**Materials and Methods**

The SHCS is an ongoing study that has been enrolling HIV-infected persons since 1984 from seven large hospitals in Switzerland (http://[www.shcs.ch](http://www.shcs.ch)), including 103,000 person years (py) of follow-up until December 2011. Detailed information on all AIDS-related disease, CD4+ cell count and HIV-related treatments are collected at enrolment, and at each six-month follow-up visit.

A total of 68 anal cancer cases were identified in SHCS participants, of whom 54 were identified from the SHCS database, and 14 additional cases were identified through record linkage with eight Swiss Cantonal Cancer Registries [Franceschi et al., 2010]. Six prevalent cases occurring before, or within 1 month of, SHCS enrollment and three diagnosed more than 6 months after the last SHCS follow-up date were excluded, leaving 59 eligible incident cases occurring during active SHCS follow-up.

For each anal cancer case, five control subjects were matched at random from eligible SHCS participants without anal cancer. Eligible controls had at least the same length of follow-up as the matched case. Matching criteria were: (1) SHCS centre; (2) gender; (3) HIV-transmission category (Injection Drug Users [IDU], MSM, heterosexual/other); (4) age at enrolment (as close as possible, up to a maximum of 9 years difference); (5) year at enrolment date (as close as possible, but within the following calendar periods: (1985-1989, 1990-1992, 1993-1995, 1996-1998, 1999-2004).

Markers of immunodeficiency (CD4+ and CD8+ cell counts; CD4+/CD8+ ratio; HIV viral load) were extracted from the SHCS database at different time periods before the reference date, defined for cases as the date of anal cancer diagnosis, and for controls as that occurring after a similar length of follow-up as the matched case prior to anal cancer. We additionally calculated median CD4+ cell counts at <1, 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-9 and 9-10 years prior to the reference date, restricted to cases and controls who 1) were under active follow-up and 2) had a valid CD4+ cell count, in each time period. If more than one measurement for any marker of immunodeficiency was available during any one time period, that closest to the reference date was used. Matching was not retained in the long-term comparison of mean CD4+ cell counts and numbers of cases and controls decreased substantially as follow-up went back in time. The nadir CD4+ cell count, defined as the lowest ever reported CD4+ cell count whilst under active SHCS follow-up, was also extracted for each subject.

cART was defined as a combination of at least three antiretroviral drugs, including a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor or three nucleosides, including abacavir. Only persons who had used cART for more than 1 month prior to the reference date were classified as users.

For a sub-set of 41 cases, as well as 114 corresponding controls, with available serum samples, HPV antibodies were tested in the serum samples taken closest in time prior to the reference date. HPV serology testing was performed at the German Cancer Research Center (DKFZ) in Heidelberg, Germany using multiplex bead-based technology (xMAP, Luminex Corp) [Waterboer et al., 2005] including the antigens for the L1 coat protein of 8 high-risk HPV types (16, 18, 31, 33, 35, 45, 52 and 58), two low-risk HPV types (6 and 11) as well as the E6 and E7 oncoproteins of HPV16. All antigens were categorized as antibody positive or negative by applying previously defined antigen-specific cutoff values [Clifford et al., 2007].

This study was approved by the local ethical committees of the seven SHCS sites and of the International Agency for Research on Cancer. Written informed consent was obtained from all SHCS participants.

Risk factors for anal cancer were evaluated by logistic regression, conditioned on matching variables, to calculate odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs).

Results

Table 1 shows the distribution of the 59 anal cancer cases and 295 controls by matching variables. A majority of anal cancer cases were MSM (72.9%); were aged 35 years or above at anal cancer diagnosis (93.2%); were diagnosed after the introduction of cART in 1996 (98.3%); and were under active follow up in the SHCS for more than five years prior to anal cancer diagnosis (79.7%).

Associations of anal cancer risk with smoking, cART use, history of AIDS and nadir CD4+ cell count are shown in Table 2. Current smoking was more frequent in cases (68.5%) than controls (47.6%) and was significantly associated with anal cancer risk (OR=2.59, 95% CI: 1.25-5.34). Although a large majority of cases (94.9%) and controls (86.8%) had a history of cART use, the association between cART use and anal cancer was not statistically significant (OR *versus* never=6.85, 95% CI: 0.90-52.4), and even less so after adjustment for nadir CD4+ cell count (OR *versus* never=4.75, 95% CI: 0.60-37.4). A history of AIDS was more frequent among cases (42.4%) than controls (30.8%), but this difference was not statistically significant either (OR = 1.72, 95% CI 0.94-3.14). Anal cancer was significantly associated with a low nadir CD4+ cell count (OR per 100 μL decrease = 1.53, 95% CI 1.18–2.00).

Figure 1 shows median CD4+ cell counts from 10 years to <1 year prior to the reference date in anal cancer cases and controls. At every time period prior to the reference date, there was evidence of a lower median CD4+ cell count in cases compared to that in controls. Greatest differences in median CD4+ count between cases and controls were at 6-7 years prior to cancer diagnosis.

The associations of various markers of immunodeficiency with anal cancer risk are shown in Table 4, measured at two different time periods with respect to anal cancer diagnosis (within 1 year and 6-7 years prior). Anal cancer was significantly associated with low CD4+ cell count when measured within 1 year of cancer diagnosis (OR per 100 μL decrease = 1.24, 95% CI 1.08-1.42), but this association was stronger when measured 6-7 years prior (OR per 100 μL decrease = 1.58, 95% CI 1.27-1.97). CD4+/CD8+ ratio was significantly associated with anal cancer when measured at 6-7 years prior (OR for <0.25 versus >0.50 = 5.23, 95% CI 2.02-13.6), but not within 1 year, of cancer diagnosis. No evidence of an association between anal cancer and HIV viral load was observed at either time point.

In a sensitivity analysis restricted to MSM only, associations between CD4+ cell count measured within 1 year of cancer diagnosis (OR per 100 μL decrease = 1.31, 95% CI 1.10-1.56), or 6-7 years prior (OR per 100 μL decrease = 2.04, 95% CI 1.44-2.88), were a little stronger than, although consistent with, overall findings (Table 3). This was also the case for associations with nadir CD4+ cell count (OR per 100 μL decrease = 1.78, 95% CI 1.28-2.48) and a history of AIDS (OR = 2.16, 95% CI 1.06-4.43).

Table 4 shows the relationship between anal cancer and serological markers of HPV. Anal cancer was significantly associated with seropositivity for antibodies against L1 coat proteins of HPV16 (OR=4.52, 95% CI 2.00-10.2), of HPV18/31/33/35/45/52/58 (OR=2.30, 95% CI 1.03-5.13) and of HPV6/11 (OR=3.04, 95% CI 1.15-8.01). Nine anal cancer cases (20%) and 0 controls were seropositive for antibodies against the E6 oncoprotein of HPV16 (OR=∞). No difference in the prevalence of antibodies against the E7 oncoprotein of HPV16 was observed between cases (2.4%) and controls (4.4%) (data not shown). Among cases, 66% of serum samples had been taken <3 months prior to cancer diagnosis, but no difference in seropositivity were seen by time of collection of the serum sample prior to cancer. Among controls, the prevalence of L1 antibodies against HPV 16, HPV18/31/33/35/45/52/58 and HPV6/11 were 41.0%, 62.8% and 69.2% for MSM, and 33.3%, 36.1%, 55.6% for IDUs/Het/Others, respectively. The prevalence of all serological HPV markers was consistent across CD4+ cell levels, both among cases and controls.

**Discussion**

Our carefully matched case–control study within the SHCS was able to confirm exposure to human papillomavirus, smoking and HIV-related immunodeficiency (as measured by low CD4+ cell count) as significant risk factors for anal cancer in HIV-positive individuals.

To our knowledge, this is the first study to look at the temporal patterns of CD4+ cell counts in relation to anal cancer risk and a novel finding was that the most predictive measure of anal cancer risk was not CD4+ cell count at cancer diagnosis [Reekie et al., 2010], nor nadir CD4+ cell count [Patel et al., 2008;Piketty et al., 2008;Crum-Cianflone et al., 2010;D'Souza et al., 2008;Powles et al., 2009], but rather the CD4+ cell count somewhere between 5 and 10 years prior to cancer diagnosis, best captured by a single CD4+ cell count measure at 6-7 years prior to cancer. Beyond this point, the risk for developing anal cancer appears to become less sensitive to CD4+ cell counts, even if they are improved by cART.

There was no evidence for a protective effect of cART, at least not as it has been used to date in the SHCS, on anal cancer risk, even though cases and controls were well matched with respect to age, year and follow-up. This is in agreement with a study from the United States showing no effect of cART use on anal cancer incidence [D'Souza et al., 2008], and many cohort studies reporting no temporal decreases in anal cancer incidence since the introduction of cART [Shiels et al., 2011;Patel et al., 2008;Piketty et al., 2008;Franceschi et al., 2010;Powles et al., 2009;van Leeuwen et al., 2009]. Indeed, many studies even report increases in anal cancer incidence since the introduction of cART [Shiels et al., 2011;Patel et al., 2008;Piketty et al., 2008;Franceschi et al., 2010], but historical trends are complicated by the substantial aging of PHIV populations in the cART era [Franceschi et al., 2010]. Although cART use also appeared to increase anal cancer risk in the SHCS, non-cART use were confounded by PHIV who had never had low CD4+ cell counts (average nadir = 355, versus 130 for cART-users).

The present study also showed that significant increases in anal cancer risk are evident even at moderate levels (200-499 CD4+ cells/μL) of immunosuppression. Hence, early initiation of cART, to avoid even moderate levels of immunosuppression among HIV-positive persons, appears important to prevent long-term risks for anal cancer.

Taken together, these data suggest that immunodefiency influences the early natural history of HPV infection, but that at some point 5 to 10 years prior to anal cancer, precancerous lesions are established, that become relatively insensitive to cART immune reconstitution. Indeed, there is accumulating evidence that high-grade AIN is a pre-cursor lesion to anal cancer [Scholefield et al., 2005;Devaraj and Cosman, 2006;Watson et al., 2006], but these clinical series are subject to selection bias, so that the time for progression is not known. In the analogous situation in the cervix, 50% of CIN3 lesions progress to cervical cancer after 30 years (Schiffman, JNCI, 2011).

The majority of anal cancer cases in the SHCS occurred among MSM, with an incidence rate above 100 cases per 100,000 person years in the cART era [Machalek et al., 2012]. Given such a high risk, anal screening of HIV+ MSM has been proposed, by identifying a group of MSM to refer for high-resolution anoscopy (HRA), and treatment of high grade anal intraepithelial lesions. However, given that many anal cancer cases occur at only moderate levels of immune suppression, CD4+ cell count history, irrespective of how and/or when it is measured, appears to be of only limited specificity to select HIV-positive MSM at highest anal cancer risk. For example, a cut-off of <200 nadir CD4+ cell count would still require the referral of the majority of MSM, whilst missing 25% of anal cancer cases. Nevertheless, given the current limited resources of HRA in most settings and the lack of a more specific marker, CD4+ count history might still have some role in identifying a sub-group of MSM at highest risk for anal cancer.

The association between current smoking and anal cancer risk confirms findings from a few previous studies in the general [Daling et al., 2004;Tseng et al., 2003;Frisch et al., 1999] and HIV-positive [D'Souza et al., 2008] population and also those from a large pooled analysis of cervical cancer [International Collaboration of Epidemiological Studies of Cervical Cancer, 2006]. Also similar to previous studies on anal and cervical cancer, no clear association was seen with former smoking in the SHCS. This suggests that smoking has a late-stage effect on HPV-induced carcinogenesis [International Collaboration of Epidemiological Studies of Cervical Cancer, 2006] and that stopping smoking can contribute to anal cancer prevention.

Cumulative exposure to HPV was confirmed to be very high in the HIV-positive population in Switzerland, particularly among MSM. Forty-one percent of MSM in the control group were seropositive for HPV16, and an additional fraction of individuals are known not to seroconvert after HPV infection [Wang et al., 2004]. This is the first study, to our knowledge, to report the seroprevalence of HPV antibodies in HIV+ve MSM, but it is consistent with an average prevalence of 35% for the detection of anal HPV16 DNA in this population [Machalek et al., 2012]. In addition to high background prevalence, all markers of HPV were significantly associated with anal cancer risk. Given that HPV16 accounts for the large majority of anal cancer, associations with other HPV types, particularly the low-risk types 6/11, are expected to represent confounding by a common route of transmission with HPV16. Only one fifth of all anal cancer cases were seropositive for antibodies against HPV16 E6, which proved to be a very specific (zero positive controls), but insensitive, marker for anal cancer, as has also been reported for cervical cancer [Zumbach et al., 2000;Meschede et al., 1998].

The SHCS has many strengths, including the duration, and regularity of follow-up and comprehensiveness of clinical and laboratory information. Approximately half of PHIV in Switzerland have been enrolled in the SHCS, and both sexes and different risk categories are well represented. Additional strengths were the supplementation of cancer diagnoses through linkage with cancer registries [Franceschi et al., 2010] and the availability of serum samples for serological analyses. The principal weaknesses of the study were the relatively small number of anal cancer cases and the lack of access to tumor tissue for HPV DNA analysis.

In conclusion, anal cancer is almost entirely HPV-related [IARC, 2012] and should be preventable. Universal HPV vaccination can be expected to prevent anal cancer risk among future cohorts of PHIV and MSM, but prophylactic vaccines will have little impact on PHIV who are already highly exposed to oncogenic HPV. Rather, avoiding even moderate levels of immunosuppression among HIV-positive persons by early initiation of cART, and smoking cessation, appear important to reduce long-term risks for anal cancer. HPV-related precancerous lesions of the anus, once established, appear to become relatively insensitive to immune reconstitution and, hence, we may yet see a favourable effect of sufficiently early cART initiation on anal cancer incidence. The same favourable effect may also hold true for the prevention of other HPV-related cancers in PHIV.

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**Table 1.** Distribution of 59 anal cancer cases and 295 control subjects according to matching variables. The Swiss HIV Cohort Study, 1985-2011.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Anal cancer** | | **Controls** | |
|  | **N** | **(%)** | **N** | **(%)** |
| **Centre** |  |  |  |  |
| Basel | 5 | (8) | 25 | (8) |
| Bern | 7 | (12) | 35 | (12) |
| Geneva | 9 | (15) | 45 | (15) |
| St Gallen | 1 | (2) | 5 | (2) |
| Vaud | 8 | (14) | 40 | (14) |
| Zurich | 29 | (49) | 145 | (49) |
|  |  |  |  |  |
| **Gender** |  |  |  |  |
| Male | 50 | (85) | 250 | (85) |
| Female | 9 | (15) | 45 | (15) |
|  |  |  |  |  |
| **HIV-transmission category** | | |  |  |
| MSM | 43 | (73) | 215 | (73) |
| IDUs | 8 | (14) | 40 | (14) |
| Het/Other | 8 | (14) | 40 | (14) |
|  |  |  |  |  |
| **Age at anal cancer a (years)** | | |  |  |
| 25-34 | 4 | (7) | 16 | (6) |
| 35-44 | 19 | (32) | 114 | (39) |
| 45-54 | 30 | (51) | 134 | (45) |
| ≥55 | 6 | (10) | 31 | (10) |
|  |  |  |  |  |
| **Calendar period at anal cancer a** | | |  |  |
| 1992-1996 | 1 | (2) | 8 | (3) |
| 1997-2001 | 16 | (27) | 85 | (29) |
| 2002-2006 | 23 | (39) | 116 | (39) |
| 2007-2011 | 19 | (32) | 86 | (29) |
|  |  |  |  |  |
| **Duration of follow-up prior to anal cancer a (years)** | | | | |
| 0-4 | 12 | (20) | 60 | (20) |
| 5-9 | 15 | (25) | 75 | (25) |
| 10-14 | 19 | (32) | 96 | (32) |
| ≥15 | 13 | (22) | 64 | (22) |
| *a*or reference date for controls (date after a similar length of follow-up in the SHCS as the matched case). MSM=Men Having Sex with Men; IDU=Intravenous Drug Users; Het=Heterosexual. | | | | |

**Table 2.** Relative risk for anal cancer by selected characteristics at reference datea. The Swiss HIV Cohort Study, 1985-2011.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Anal cancer** | | **Controls** | | **ORb**  **(95% CI)** |
|  | **N** | **(%)** | **N** | **(%)** |  |
| Overall | 59 |  | 295 |  |  |
|  |  |  |  |  |  |
| **Smoking status** | |  |  |  |  |
| Never | 12 | (22) | 100 | (37) | 1 |
| Former | 5 | (9) | 43 | (16) | 0.96 (0.32-2.89) |
| Current | 37 | (69) | 130 | (48) | 2.59 (1.25-5.34) |
|  |  |  |  |  |  |
| **History of cART use** | | |  |  |  |
| Never | 3 | (5) | 39 | (13) | 1 |
| Ever | 56 | (95) | 256 | (87) | 6.85 (0.90-52.4) |
|  | | | | |  |
| **History of AIDS** | | | | |  |
| No | 34 | (58) | 204 | (69) | 1 |
| Yes | 25 | (42) | 91 | (31) | 1.72 (0.94-3.14) |
|  |  |  |  |  |  |
| **Nadir CD4+ cell count, cells/μL** | | | |  |  |
| ≥200 | 15 | (25) | 125 | (42) | 1 |
| 50-199 | 20 | (34) | 113 | (38) | 1.68 (0.77-3.65) |
| <50 | 24 | (41) | 57 | (19) | 3.96 (1.82-8.61) |
|  |  |  |  |  |  |
| Per 100 μL decrease | | |  |  | 1.53 (1.18–2.00) |
| aSee Materials and Methods section for definition of reference date; bConditioned upon matching variables. OR=odds ratio; CI=confidence interval; cART=combined antiretroviral therapy. | | | | | |

**Table 3.** Relative risk for anal cancer, by markers of immunodeficiency at two different time periods prior to cancer diagnosis. The Swiss HIV Cohort Study, 1985-2011.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Six-seven years before anal cancera** | | | | | **Within one year before anal cancera** | | | | | | | | |
|  | **Anal cancer** | | **Controls** | | **ORb**  **(95% CI)** | | **Anal cancer** | | | **Controls** | | | **ORb**  **(95% CI)** | |
|  | **N** | **(%)** | **N** | **(%)** | **N** | **%** | | **N** | **%** | |
| **Overall** | 59 |  | 295 |  |  | | 59 |  | | 295 |  | |  | |
|  |  |  |  |  |  | |  |  | |  |  | |  | |
| **CD4+ cell count, cells/μL** | | | | |  | |  |  | |  |  | |  | |
| >500 | 3 | (8) | 69 | (37) | 1 | | 16 | (28) | | 134 | (47) | | 1 | |
| 200-499 | 16 | 41.0 | 87 | 46.8 | 4.42 (1.19-16.4) | | 30 | 51.7 | | 127 | 44.2 | | 2.13 (1.10-4.13) | |
| <200 | 20 | (51) | 30 | (16) | 14.0 (3.85-50.9) | | 12 | (21) | | 26 | (9) | | 4.56 (1.81-11.4) | |
| Unknown | 20 |  | 109 |  |  | | 1 |  | | 8 |  | |  | |
|  |  |  |  |  |  | |  |  | |  |  | |  | |
| Per 100 μL decrease | | |  |  | 1.58 (1.27-1.97) | |  |  | |  |  | | 1.24 (1.08-1.42) | |
|  |  |  |  |  |  | |  |  | |  |  | |  | |
| **CD8+ cell count, cells/μL** | | | | |  | |  |  | |  |  | |  | |
| >1000 | 10 | (26) | 82 | (44) | 1 | | 24 | (41) | | 126 | (44) | | 1 | |
| 500-999 | 23 | (59) | 79 | (42) | 2.47 (1.09-5.60) | | 28 | (48) | | 130 | (45) | | 1.13 (0.61-2.06) | |
| <500 | 6 | (15) | 25 | (13) | 2.06 (0.66-6.40) | | 6 | (10) | | 31 | (11) | | 1.01 (0.36-2.80) | |
| Unknown | 20 |  | 109 |  |  | | 1 |  | | 8 |  | |  | |
|  |  |  |  |  |  | |  |  | |  |  | |  | |
| **CD4+/CD8+ ratio** | | | | |  | |  |  | |  |  | |  | |
| >0.50 | 7 | (19) | 74 | (41) | 1 | | 20 | (35) | | 141 | (49) | | 1 | |
| 0.25-0.49 | 10 | (27) | 65 | (36) | 1.58 (0.57-4.38) | | 26 | (45) | | 95 | (33) | | 1.91 (1.02-3.58) | |
| <0.25 | 20 | (54) | 41 | (23) | 5.23 (2.02-13.6) | | 12 | (21) | | 51 | (18) | | 1.72 (0.76-3.87) | |
| Unknown | 22 |  | 115 |  |  | | 1 |  | | 8 |  | |  | |
|  |  |  |  |  |  | |  |  | |  |  | |  | |
| **HIV Viral load, copies/mL** | | | | |  |  | | |  |  |  |  | | |
| <500 | 19 | (61) | 102 | (67) | 1 | 39 | | | (70) | 208 | (76) | 1 | | |
| 500-9,999 | 5 | (16) | 22 | (14) | 1.23 (0.40-3.76) | 6 | | | (11) | 33 | (12) | 1.08 (0.41-2.81) | | |
| >10,000 | 7 | (23) | 29 | (19) | 1.27 (0.50-3.21) | 11 | | | (20) | 32 | (12) | 1.90 (0.85-4.23) | | |
| Unknown | 28 |  | 142 |  |  | 3 | | |  | 22 |  |  | | |
|  |  |  |  |  |  |  | | |  |  |  |  | | |
| **MSM only** | 43 |  | 215 |  |  | 43 | | |  | 215 |  |  | | |
|  |  |  |  |  |  |  | | |  |  |  |  | | |
| **CD4+ cell count, cells/μL** | | | | |  |  | | |  |  |  |  | | |
| >500 | 2 | (7) | 52 | (41) | 1 | 11 | | | (26) | 103 | (49) | 1 | | |
| 200-499 | 9 | (32) | 55 | (44) | 4.59 (0.93-22.7) | 23 | | | (54) | 95 | (45) | 2.64 (1.17-5.98) | | |
| <200 | 17 | (61) | 19 | (15) | 29.0 (5.79-145) | 9 | | | (21) | 13 | (6) | 8.69 (2.66-28.5) | | |
| Unknown | 15 |  | 89 |  |  | 0 | | |  | 4 |  |  | | |
|  |  |  |  |  |  |  | | |  |  |  |  | | |
| Per 100 μL decrease | | |  |  | 2.04 (1.44-2.88) |  | | |  |  |  | 1.31 (1.10-1.56) | | |
|  |  |  |  |  |  |  | | |  |  |  |  | | |
| aor before the reference date in controls (see Materials and Methods for definition); bconditioned upon matching variables. OR=odds ratio; CI=confidence interval | | | | | | | | | | | | | |

**Figure 1.** Box plotsa of CD4+ cell counts at yearly intervals prior to reference dateb, among anal cancer cases and controls. The Swiss HIV Cohort Study, 1985-2011.

aHorizontal lines in boxplots represent 10th, 25th, 50th (median), 75th and 90th percentiles.

bSeePatients and Methods for definition of reference date.

**Table 4.** Relative risk for anal cancer by seropositivity for selected HPV antigens among 41 cases and 114 matched controls. The Swiss HIV Cohort Study, 1985-2011.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| HPV antigen | **Anal cancer** | | **Controls** | | **ORa**  **(95% CI)** |
| **N** | **(%)** | **N** | **(%)** |  |
| Overall | 41 |  | 114 |  |  |
|  |  |  |  |  |  |
| **L1** |  |  |  |  |  |
| **HPV-16** |  |  |  |  |  |
| Seronegative | 10 | (24) | 70 | (61) | 1 |
| Seropositive | 31 | (76) | 44 | (39) | 4.52 (2.00-10.2) |
|  |  |  |  |  |  |
| **Any other (non-HPV16) high-risk HPV b** | | |  |  |  |
| Seronegative | 11 | (27) | 52 | (46) | 1 |
| Seropositive | 30 | (73) | 62 | (54) | 2.30 (1.03-5.13) |
|  |  |  |  |  |  |
| **HPV6/11** |  |  |  |  |  |
| Seronegative | 7 | (17) | 40 | (35) | 1 |
| Seropositive | 34 | (83) | 74 | (65) | 3.04 (1.15-8.01) |
|  |  |  |  |  |  |
| **E6** |  |  |  |  |  |
| **HPV-16** |  |  |  |  |  |
| Seronegative | 32 | (78) | 114 | (100) | 1 |
| Seropositive | 9 | (22) | 0 | (0) | ∞ |
|  |  |  |  |  |  |
| aConditioned upon matching variables;  bSeropositive with any of HPV L1 antigens (18, 31, 33, 35, 45, 52 or 58). | | | | | |

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