

Original Contribution

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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Initially submitted October 22, 2012; accepted for publication February 21, 2013.

Although persons infected with human immunodeficiency virus (HIV), particularly men who have sex with men, 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. A case-control study that included 59 anal cancer cases and 295 individually matched controls was nested in the Swiss HIV Cohort Study (1988–2011). In a subset of 41 cases and 114 controls, HPV antibodies were tested. A majority of anal cancer cases (73%) were men who have sex with men. Current smoking was significantly associated with anal cancer (odds ratio (OR) = 2.59, 95% confidence interval (CI): 1.25, 5.34), as were antibodies against L1 (OR = 4.52, 95% CI: 2.00, 10.20) and E6 (OR = ∞, 95% CI: 4.64, ∞) of HPV16, as well as low CD4+ cell counts, whether measured at nadir (OR per 100-cell/ μ L decrease = 1.53, 95% CI: 1.18, 2.00) or at cancer diagnosis (OR per 100-cell/ μ L decrease = 1.24, 95% CI: 1.08, 1.42). However, the influence of CD4+ cell counts appeared to be strongest 6–7 years prior to anal cancer diagnosis (OR for <200 vs. \geq 500 cells/ μ L = 14.0, 95% CI: 3.85, 50.9). Smoking cessation and avoidance of even moderate levels of immunosuppression appear to be important in reducing long-term anal cancer risks.

anal cancer; case-control study; HIV; human papillomavirus; immunodeficiency

Abbreviations: AIDS, acquired immunodeficiency syndrome; cART, combined antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; HPV, human papillomavirus; MSM, men who have sex with men; OR, odds ratio; SHCS, Swiss HIV Cohort Study.

Editor's note: An invited commentary on this article appears on page 885, and the authors' response appears on page 888.

In the Swiss HIV Cohort Study (SHCS) (1), as in other studies of persons infected with human immunodeficiency virus (HIV) (2), there is a 30-fold higher rate of anal cancer in comparison with the general population. Anal cancer incidence is particularly high among, but not limited to, men who have sex with men (MSM) (3), for whom incidence

estimates exceed 100 per 100,000 person-years in the era of combined antiretroviral therapy (cART) (4, 5).

Anal cancer is a consequence of infection with high-risk human papillomavirus (HPV) types, mainly HPV16 (6). However, in addition to increased sexual exposure to anal HPV infection, excess risk in persons infected with HIV likely reflects the influence of immunodeficiency on the natural history of HPV. Immunodeficiency has been linked to increased anal cancer risk by using the measures of CD4+ counts at cancer diagnosis (7) or at the beginning of follow-up (5), of the duration of CD4+ cell counts below 200/ μ L (8, 9), and

of nadir CD4+ counts (10–14). However, it is still not well understood when in the long evolution from HPV infection to anal cancer development the influence of immunodeficiency is most important.

The effect of cART-related improvements in immunity on anal cancer risk also remains unclear. Although some cohort studies of persons infected with HIV have reported strong increases in anal cancer incidence since the introduction of cART (1, 10, 11, 15, 16), others have not (14, 17). Historical trends are additionally complicated by the vast increase in the life expectancy of persons infected with HIV in the cART era, because anal cancer incidence increases exponentially with age (1).

Thus, we undertook a case-control study nested within the SHCS, specifically designed to characterize the influence of immunodeficiency and cART on the development of anal cancer among persons infected with HIV.

MATERIALS AND METHODS

The SHCS is an ongoing study that has been enrolling persons infected with HIV since 1988 from 7 large hospitals in Switzerland (<http://www.shcs.ch>) (18), representing 103,000 person-years of follow-up until December 2011. Detailed information on all acquired immunodeficiency syndrome (AIDS)-related diseases, CD4+ cell counts, and HIV-related treatments is collected at enrollment and at each 6-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 through record linkage with 8 Swiss cantonal cancer registries (1, 3). Six prevalent cases occurring before or within 1 month of SHCS enrollment and 3 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, 5 control subjects were matched at random by using incidence density sampling from SHCS participants who were never diagnosed with anal cancer. Each control had at least the same length of follow-up as its matched case and could serve as a control for only 1 case. Matching criteria were: 1) SHCS center; 2) sex; 3) HIV transmission category (i.e., intravenous drug users, MSM, heterosexuals/others); 4) age at enrollment (as close as possible, up to a maximum of 9 years' difference); and 5) year at enrollment date (as close as possible, but at least within the following calendar periods: 1985–1989, 1990–1992, 1993–1995, 1996–1998, or 1999–2004).

Markers of immunodeficiency (i.e., CD4+ and CD8+ cell counts, CD4+/CD8+ ratios, and HIV viral loads) were extracted from the SHCS database at different time periods before the reference date, which was defined for cases as the date of anal cancer diagnosis and for controls as the date after the same length of follow-up in the SHCS as that for the matched case at anal cancer diagnosis. Additionally, we calculated median CD4+ cell counts in 12-month periods prior to the reference date, restricted to cases and controls who were under active follow-up and who had valid CD4+ cell counts in each time period. If more than 1 measurement for any marker of immunodeficiency was available during

any 1 time period, that closest to the reference date was used. Matching was not retained in the long-term comparison of mean CD4+ cell counts because 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, was also extracted for each subject.

cART was defined as a combination of at least 3 antiretroviral drugs, including either a protease inhibitor and a non-nucleoside reverse transcriptase inhibitor or 3 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 subset of 41 cases, as well as for 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 in Heidelberg, Germany, by using multiplex bead-based technology (xMAP, Luminex Corp., Austin, Texas) (19) including the antigens for the L1 coat protein of HPV16, 7 additional high-risk HPV types (18, 31, 33, 35, 45, 52 and 58), and 2 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 (20).

This study was approved by the local ethics committees of the 7 SHCS sites and of the International Agency for Research on Cancer. Written informed consent was obtained from all SHCS participants.

Odds ratios and corresponding 95% confidence intervals for possible risk factors for anal cancer were computed by logistic regression, conditioned on matching variables.

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 (73%), aged 35 years or older at anal cancer diagnosis (93%), diagnosed after the introduction of cART in 1996 (98%), and under active follow-up in the SHCS for more than 5 years prior to anal cancer diagnosis (80%).

Associations of anal cancer risk with smoking, cART use, history of AIDS, and nadir CD4+ cell counts are shown in Table 2. Current (but not former) smoking was more frequent in cases (69%) than in controls (48%) and was significantly associated with anal cancer risk (odds ratio (OR) = 2.59, 95% confidence interval (CI): 1.25, 5.34). Because the vast majority of cases (95%) and controls (87%) had a history of cART use, the association between cART use and anal cancer has very broad confidence intervals (OR for ever vs. never = 6.85, 95% CI: 0.90, 52.40) and was attenuated by adjustment for nadir CD4+ cell count (OR for ever vs. never = 4.75, 95% CI: 0.60, 37.40) (data not shown). A history of AIDS was more frequent among cases (42%) than controls (31%), but this difference was not statistically significant (OR = 1.72, 95% CI: 0.94, 3.14). Anal cancer was significantly associated with a low nadir CD4+ cell count (OR per 100-cell/ μ L decrease = 1.53, 95% CI: 1.18, 2.00).

Table 1. Distribution of 59 Anal Cancer Cases and 295 Control Subjects According to Matching Variables, Swiss HIV Cohort Study, 1988–2011

Matching Variable	Cases		Controls	
	No.	%	No.	%
Sex				
Men	50	85	250	85
Women	9	15	45	15
HIV transmission category				
MSM	43	73	215	73
IV drug users	8	14	40	14
Heterosexuals/others	8	14	40	14
Age at anal cancer, years ^a				
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 diagnosis ^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, years ^a				
0–4	12	20	60	20
5–9	15	25	75	25
10–14	19	32	96	32
≥15	13	22	64	22

Abbreviations: HIV, human immunodeficiency virus; IV, intravenous; MSM, men who have sex with men.

^a Or reference date for controls (date after the same length of follow-up in the Swiss HIV Cohort Study as the matched case).

Figure 1 shows median CD4+ cell counts in 12-month periods prior to the reference date in anal cancer cases and controls. At every time period prior to the reference date, there was evidence of lower median CD4+ cell counts in cases compared with those in controls. The greatest differences in median CD4+ counts between cases and controls were at 72–83 months (6–7 years) prior to cancer diagnosis.

The associations of various markers of immunodeficiency with anal cancer risk, measured at 2 different time periods with respect to the reference date (within 1 year prior and 6–7 years prior), are shown in Table 3. Anal cancer was significantly associated with low CD4+ cell counts when measured within 1 year of cancer diagnosis (OR for <200 vs. ≥500 cells/μL = 4.56, 95% CI: 1.81, 11.40), but this association appeared stronger when measured 6–7 years prior (OR for <200 vs. ≥500 cells/μL = 14.0, 95% CI: 3.85, 50.9). The CD4+/CD8+ ratio was strongly and significantly associated with anal cancer when measured 6–7 years prior to cancer diagnosis (OR for <0.25 vs. >0.50 = 5.23, 95% CI: 2.02,

Table 2. Odds Ratios for Anal Cancer by Selected Characteristics at Reference Date,^a Swiss HIV Cohort Study, 1988–2011

	Cases		Controls		OR ^b	95% CI
	No.	%	No.	%		
Overall	59		295			
Smoking status						
Never	12	22	100	37	1	Referent
Former	5	9	43	16	0.96	0.32, 2.89
Current	37	69	130	48	2.59	1.25, 5.34
Unknown	5		22			
History of cART use						
Never	3	5	39	13	1	Referent
Ever	56	95	256	87	6.85	0.90, 52.40
History of AIDS						
No	34	58	204	69	1	Referent
Yes	25	42	91	31	1.72	0.94, 3.14
Nadir CD4+ cell count, cells/μL						
≥200	15	25	125	42	1	Referent
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-cell/μL decrease					1.53	1.18, 2.00

Abbreviations: AIDS, acquired immunodeficiency syndrome; cART, combined antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

^a Reference date was defined for cases as the date of anal cancer diagnosis and for controls as the date after the same length of follow-up in the SHCS as that for the matched case at anal cancer.

^b Conditioned on matching variables.

13.60) but not within 1 year prior to cancer diagnosis (OR for <0.25 vs. >0.50 = 1.72, 95% CI: 0.76, 3.87). No evidence of an association between anal cancer and HIV viral load was observed at either time point. None of these associations was affected by residual confounding by age, because they did not materially change when age was included as a continuous variable in the model (data not shown).

In a sensitivity analysis restricted to MSM, associations between CD4+ cell counts measured within 1 year of cancer diagnosis (OR per 100-cell/μL decrease = 1.31, 95% CI: 1.10, 1.56), or 6–7 years prior (OR per 100-cell/μL decrease = 2.04, 95% CI: 1.44, 2.88) were a little stronger than, although consistent with, the overall findings (Table 3). This was also the case for associations with nadir CD4+ cell counts (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) (data not shown).

Table 4 shows the relationship between anal cancer risk and serological markers of HPV. Anal cancer risk was significantly associated with seropositivity for antibodies against L1 coat proteins of HPV16 (OR = 4.52, 95% CI: 2.00, 10.20), of HPV18, 31, 33, 35, 45, 52, and 58 (OR = 2.30, 95% CI: 1.03, 5.13), and of HPV6 and 11 (OR = 3.04, 95% CI: 1.15, 8.01). Nine anal cancer cases (22%) and 0 controls were seropositive for antibodies against the E6 oncoprotein

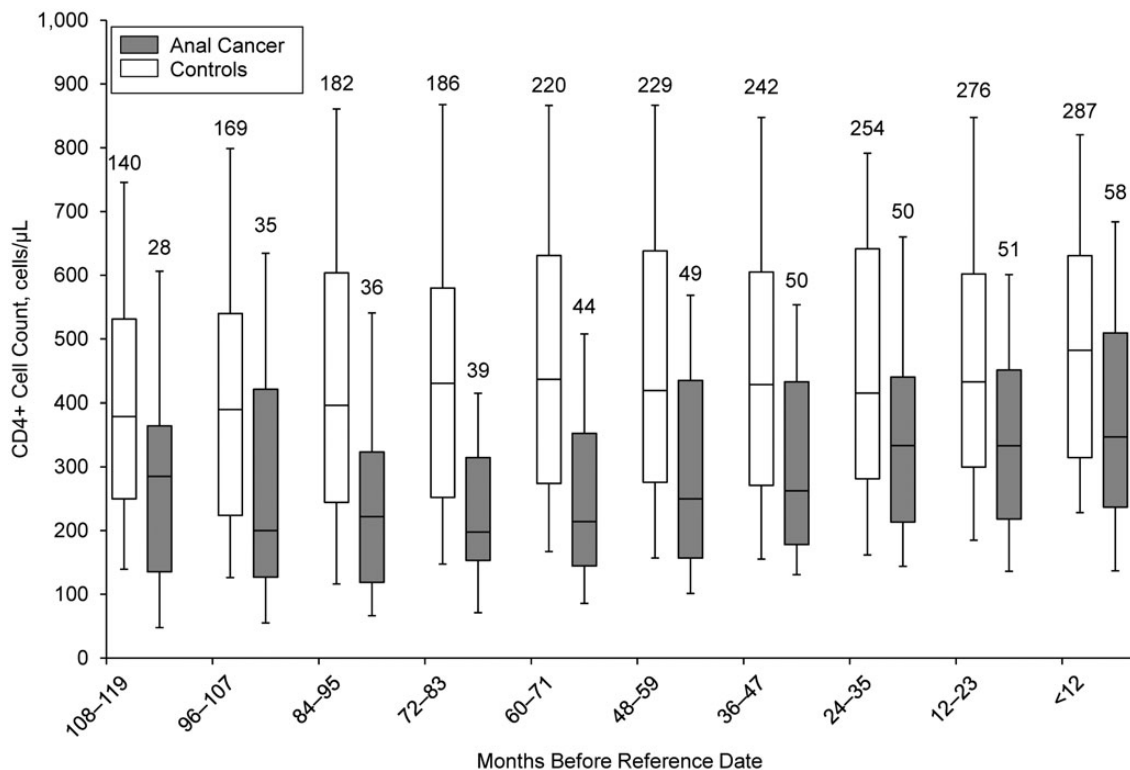


Figure 1. Box plots of CD4+ cell counts measured at monthly intervals prior to the reference date among anal cancer cases and controls in the Swiss HIV Cohort Study (SHCS), 1988–2011. (Reference date was defined for cases as the date of anal cancer diagnosis and for controls as the date after the same length of follow-up in the SHCS as that for the matched case at anal cancer.) Horizontal lines in the box plot represent the 10th, 25th, 50th (median), 75th, and 90th percentiles. Numbers above the box plots represent denominators. Whiskers represent 95% confidence intervals.

of HPV16 (OR = ∞ , 95% CI: 4.64, ∞). No difference in the prevalence of antibodies against the E7 oncoprotein of HPV16 was observed between cases (2%) and controls (4%) (data not shown). Among controls, the prevalence rates of L1 antibodies against HPV16, HPV18, 31, 33, 35, 45, 52, and 58, and HPV6 and 11 were 41%, 63%, and 69% for MSM and 33%, 36%, and 56% for intravenous drug users/heterosexuals/others, respectively, but were not associated with age, smoking, AIDS, or nadir CD4+ cell counts (data not shown).

DISCUSSION

Our carefully matched case-control study within the SHCS was able to show that exposure to HPV, smoking, and low CD4+ cell counts are significant risk factors for anal cancer in HIV-positive individuals.

There was no evidence for a protective effect of cART on anal cancer risk, at least not as it has been used to date in the SHCS, even though cases and controls were well matched with respect to age, year at SHCS enrollment, and length of follow-up. This is in agreement with a study from the United States showing no effect of cART use on anal cancer incidence (13) and with many cohort studies reporting no tem-

poral decreases in anal cancer incidence since the introduction of cART (1, 10, 11, 14, 15, 17). Indeed, many studies even report increases in anal cancer incidence since the introduction of cART (1, 10, 11, 15), but historical trends are complicated by the substantial aging of populations of persons infected with HIV in the cART era (1). Although cART use also appeared to increase anal cancer risk in the SHCS, non-cART users were very few and had higher CD4+ cell counts (average nadir = 355 cells/ μ L) than cART users (average nadir = 130 cells/ μ L).

To our knowledge, this is the first study to examine the temporal patterns of CD4+ cell counts in relationship to anal cancer risk. A novel finding was that the most predictive measure of anal cancer risk was not CD4+ cell count at cancer diagnosis (7), nor nadir CD4+ cell count (10–14), but rather the CD4+ cell count somewhere between 5–9 years prior to cancer diagnosis, best captured by a single CD4+ cell count measurement 6–7 years prior to cancer diagnosis. Beyond this point, the risk for developing anal cancer appears to become less sensitive to CD4+ cell counts, even if counts are improved by cART. The present study also showed that increases in anal cancer risk are evident even at moderate levels (200–499 CD4+ cells/ μ L) of immunosuppression. Hence, early initiation of cART appears to be important to prevent long-term risks for anal cancer.

Table 3. Odds Ratios for Anal Cancer by Markers of Immunodeficiency at 2 Different Time Periods Prior to Cancer Diagnosis, Swiss HIV Cohort Study, 1988–2011

Immunodeficiency Marker	72–83 Months (6–7 Years) Before Anal Cancer Diagnosis ^a						Within 12 Months Before Anal Cancer Diagnosis ^a					
	Cases		Controls		OR ^b	95% CI	Cases		Controls		OR ^b	95% CI
	No.	%	No.	%			No.	%	No.	%		
Overall	59		295				59		295			
CD4+ cell count, cells/ μ L												
≥ 500	3	8	69	37	1	Referent	16	28	134	47	1	Referent
350–499	5	13	43	23	2.83	0.62, 13.00	13	22	59	21	2.03	0.90, 4.57
200–349	11	28	44	24	5.86	1.49, 23.00	17	29	68	24	2.20	1.05, 4.59
<200	20	51	30	16	14.00	3.85, 50.90	12	21	26	9	4.56	1.81, 11.40
Unknown	20		109				1		8			
Per 100-cell/ μ L decrease					1.58	1.27, 1.97					1.24	1.08, 1.42
CD8+ cell count, cells/ μ L												
$\geq 1,000$	10	26	82	44	1	Referent	24	41	126	44	1	Referent
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	Referent	20	35	141	49	1	Referent
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, 13.60	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	Referent	39	70	208	76	1	Referent
500–9,999	5	16	22	14	1.23	0.40, 3.76	6	11	33	12	1.08	0.41, 2.81
$\geq 10,000$	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/ μ L												
≥ 500	2	7	52	41	1	Referent	11	26	103	49	1	Referent
200–499	9	32	55	44	4.59	0.93, 22.70	23	54	95	45	2.64	1.17, 5.98
<200	17	61	19	15	29.00	5.79, 145.00	9	21	13	6	8.69	2.66, 28.50
Unknown	15		89				0		4			
Per 100 cells/ μ L decrease					2.04	1.44, 2.88					1.31	1.10, 1.56

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; MSM, men who have sex with men; OR, odds ratio.

^a Or before the reference date in controls. Reference date was defined for controls as the date occurring after the same length of follow-up as the matched case prior to anal cancer diagnosis.

^b Conditioned on matching variables.

Taken together, these data suggest that immunodeficiency influences the early natural history of HPV infection, but that at some point 5–9 years prior to anal cancer diagnosis, precancerous lesions that become relatively insensitive to cART-mediated immune reconstitution are established. Indeed, there is evidence that high-grade anal intraepithelial neoplasia is a

precursor lesion to anal cancer (21–23). The probability of progression to high-grade anal intraepithelial neoplasia, however, is not known. In an analogous situation, an estimated 50% of cervical intraepithelial neoplasia grade-3 lesions in immunocompetent women progress to cervical cancer after 30 years (24).

Table 4. Odds Ratios for Anal Cancer by Seropositivity for Selected HPV Antigens Among 41 Cases and 114 Matched Controls, Swiss HIV Cohort Study, 1988–2011

HPV Antigen	Cases		Controls		OR ^a	95% CI
	No.	%	No.	%		
Overall	41		114			
L1						
HPV16						
Seronegative	10	24	70	61	1	Referent
Seropositive	31	76	44	39	4.52	2.00, 10.20
Any other (non-HPV16) high-risk HPV ^b						
Seronegative	11	27	52	46	1	Referent
Seropositive	30	73	62	54	2.30	1.03, 5.13
HPV6/11						
Seronegative	7	17	40	35	1	Referent
Seropositive	34	83	74	65	3.04	1.15, 8.01
E6						
HPV16						
Seronegative	32	78	114	100	1	Referent
Seropositive	9	22	0	0	∞	4.64, ∞

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HPV, human papillomavirus; OR, odds ratio.

^a Conditioned on matching variables.

^b Seropositive with any HPV L1 antigen (i.e., 18, 31, 33, 35, 45, 52 or 58).

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 (4). Given such a high risk, anal screening of HIV-positive MSM has been proposed (25), which would involve the identification of a group of MSM to refer for high-resolution anoscopy 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 risk for anal cancer. For example, a nadir CD4+ cell count cut-off of 200 cells/ μ L or fewer would still require the referral of the majority of MSM but would have missed 25% of anal cancer cases in the SHCS. Given the currently limited high-resolution anoscopy resources in most settings and the lack of a more specific marker, CD4+ cell count history might still have some role in identifying a subgroup of MSM at highest risk for anal cancer. Nevertheless, the most useful screening criterion was shown to be age, with anal cancer shown to be very rare in HIV-infected persons under age 35 years.

The association between current smoking and anal cancer risk confirms findings from previous studies in the general population (26–28) and in persons infected with HIV (13) and also those from a large pooled analysis of cervical cancer (29). As in previous studies of 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 (29), 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. Furthermore, an additional fraction of individuals may not seroconvert after HPV infection (30). This is the first study, to our knowledge, to report the seroprevalence of HPV antibodies in HIV-positive MSM, and it is consistent with an average prevalence of 35% for the detection of anal HPV16 DNA in this population (4). 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 and 11, are expected to derive from the 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 (0 positive controls), but insensitive, marker for anal cancer, as it has also been reported to be for cervical cancer (31, 32).

The SHCS has many strengths, including the duration and regularity of follow-up and the comprehensiveness of clinical and laboratory information. Approximately half of persons infected with HIV 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 (1) 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. Although serological assays may detect cross-reacting antibodies to other HPV types and/or reflect HPV infection at a nonanal site, these limitations should only attenuate the strength of associations.

In conclusion, anal cancer is almost entirely HPV-related (6) and should be preventable. HPV vaccination of adolescent girls and boys can be expected to prevent anal cancer risk among future cohorts of persons infected with HIV and among MSM, but prophylactic vaccines will have little impact on persons infected with HIV who are already highly exposed to oncogenic HPV. Rather, the avoidance of even moderate levels of immunosuppression among persons infected with HIV by early diagnosis and initiation of cART and by smoking cessation appears to be important to reducing 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 favorable effect of sufficiently early cART initiation on anal cancer incidence. The same favorable effect may also hold true for the prevention of other HPV-related cancers in persons infected with HIV.

ACKNOWLEDGMENTS

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St. Gallen, Switzerland (Barbara Bertisch, Pietro Vernazza); International Agency for Research on Cancer, Lyon, France (Silvia Franceschi, Mauro Lise, Gary Clifford); Epidemiology and Biostatistics Unit, Scientific Directorate, National Cancer Institute, Aviano, Italy (Mauro Lise); Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland (Olivia Keiser, Franziska Schöni-Affolter, Gilles Wandeler); Coordination and Data Center, Swiss HIV Cohort Study, Lausanne, Switzerland (Franziska Schöni-Affolter); Cancer Registry of the Canton of Geneva, Geneva, Switzerland (Christine Bouchardy); Cancer Registry of the Canton of Zurich, Zurich, Switzerland (Silvia Dehler); Cancer Registry of the Canton of Vaud, Lausanne, Switzerland (Fabio Levi); Cancer Registry of Basel, Basel, Switzerland (Gernot Jundt); Cancer Registry of St. Gallen and Appenzell, St. Gallen, Switzerland (Silvia Ess); Department of Genome Modifications and Carcinogenesis, Infection and Cancer Program, German Cancer Research Center, Heidelberg, Germany (Michael Pawlita); Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland (Helen Kovari); Department of Infectious Diseases, HIV/AIDS Unit, Bern University Hospital and University of Bern, Bern, Switzerland (Gilles Wandeler); University Clinic of Infectious Diseases, University Hospital of Geneva, Geneva, Switzerland (Alexandra Calmy); Service of Infectious Diseases, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (Matthias Cavassini); and Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland (Marcel Stöckle).

This study was performed within the framework of the Swiss HIV Cohort Study (SHCS-project 676), supported by the Swiss National Science Foundation (grant 3347-069366), and assisted by grants from OncoSuisse (ICP OCS 01355-03-2003, KFS-02478-08-2009). Mauro Lise received a fellowship from the Associazione Italiana per la Ricerca sul Cancro carried out at the International Agency for Research on Cancer.

We thank Dr. Kristina Michael for support in the serological analyses, as well as Drs. Luigino Dal Maso and Jerry Polesel for data linkage between the Swiss HIV Cohort Study and cancer registries.

The members of the Swiss HIV Cohort Study are Vincent Aubert, Jürgen Barth, Manuel Battegay, Enos Bernasconi, Jürg Böni, Heiner C. Bucher, Claudine Burton-Jeangros, Alexandra Calmy, Matthias Cavassini, Matthias Egger, Luigia Elzi, Jan Fehr, Jacques Fellay, Patrick Francioli, Hansjakob Furrer (Chairman of the Clinical and Laboratory Committee), Christoph A. Fux, Meri Gorgievski, Huldrych Günthard (President of the Swiss HIV Cohort Study), David Haerry (Deputy of "Positive Council"), Barbara Hasse, Hans H. Hirsch, Bernard Hirschel, Irène Hösli, Christian Kahlert, Laurent Kaiser, Olivia Keiser, Christian Kind, Thomas Klimkait, Helen Kovari, Bruno Ledergerber, Gladys Martinetti, Begona Martinez de Tejada, Karin Metzner, Nicolas Müller, David Nadal, Giuseppe Pantaleo, Andri Rauch (Chairman of the Scientific Board), Stephan Regenass, Martin Rickenbach (Head of the Data Center), Christoph Rudin (Chairman of the Mother and Child Substudy), Patrick Schmid, Detlev Schultze, Franziska Schöni-Affolter, Jörg

Schüpbach, Roberto Speck, Patrick Taffé, Philip Tarr, Amalio Telenti, Alexandra Trkola, Pietro Vernazza, Rainer Weber, and Sabine Yerly.

Conflict of interest: none declared.

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