Cancer Risk in the Swiss HIV Cohort Study: Associations With Immunodeficiency, Smoking, and Highly Active Antiretroviral Therapy

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Background: Persons infected with human immunodeficiency virus (HIV) have an increased risk for several cancers, but the influences of behavioral risk factors, such as smoking and intravenous drug use, and highly active antiretroviral therapy (HAART) on cancer risk are not clear. *Methods:* Patient records were linked between the Swiss HIV Cohort Study and Swiss cantonal cancer registries. Observed and expected numbers of incident cancers were assessed in 7304 persons infected with HIV followed for 28836 person-years. Relative risks for cancer compared with those for the general population were determined by estimating cancer registry–, sex-, age-, and period-standardized incidence ratios (SIRs). *Results:* Highly elevated SIRs were confirmed in persons infected with HIV for Kaposi sarcoma (KS) (SIR = 192, 95% confidence interval [CI] = 170 to 217) and non-Hodgkin lymphoma (SIR = 76.4, 95% CI = 66.5 to 87.4). Statistically significantly elevated SIRs were also observed for anal cancer (SIR = 33.4, 95% CI = 10.5 to 78.6); Hodgkin lymphoma (SIR = 17.3, 95% CI = 10.2 to 27.4); cancers of the cervix (SIR = 8.0, 95% CI = 2.9 to 17.4); liver (SIR = 7.0, 95% CI = 2.2 to 16.5); lip, mouth, and pharynx (SIR = 4.1, 95% CI = 2.1 to 7.4); trachea, lung, and bronchus (SIR = 3.2, 95% CI = 1.7 to 5.4); and skin, non-melanomatous (SIR = 3.2, 95% CI = 2.2 to 4.5). In HAART users, SIRs for KS (SIR = 25.3, 95% CI = 10.8 to 50.1) and non-Hodgkin lymphoma (SIR = 24.2, 95% CI = 15.0 to 37.1) were lower than those for nonusers (KS SIR = 239, 95% CI = 211 to 270; non-Hodgkin lymphoma SIR = 99.3, 95% CI = 85.8 to 114). Among HAART users, however, the SIR (although not absolute numbers) for Hodgkin lymphoma (SIR = 36.2, 95% CI = 16.4 to 68.9) was comparable to that for KS and non-Hodgkin lymphoma. No clear impact of HAART on SIRs emerged for cervical cancer or non–acquired immunodeficiency syndrome-defining cancers. Cancers of the lung, lip, mouth, or pharynx were not observed among nonsmokers. *Conclusion:* In persons infected with HIV, HAART use may prevent most excess risk of KS and non-Hodgkin lymphoma, but not that of Hodgkin lymphoma and other non–acquired immunodeficiency syndrome-defining cancers. No cancers of the lip, mouth, pharynx, or lung were observed in nonsmokers. [J Natl Cancer Inst 2005;97:425–32]

Record linkage studies of population-based registries of people with acquired immunodeficiency syndrome (AIDS) and cancer (1–5) have estimated excess cancer risk for people with AIDS compared with that for the general population. In particular, these studies have consistently reported elevated risks for cancers linked to oncogenic viruses, including the AIDS-defining cancers Kaposi sarcoma (KS), non-Hodgkin lymphoma, and, to a lesser extent, invasive cervical cancer, anal cancer, and Hodgkin lymphoma (1,2,4). Excesses of other cancers, such as skin, lung, and liver, have been less consistently reported. However, most linkage studies lack important individual data on confounding behavioral risk factors, on biologic markers of immune status, and on the use of highly active antiretroviral therapy (HAART), which has had a great impact on the morbidity and mortality of persons infected with human immunodeficiency virus (HIV) (6,7). Uncertainties also stem from the possible biases produced when data are extrapolated from AIDS registries to estimate the risk for all persons infected with HIV, some of whom may never develop AIDS before cancer or death (8).

Conversely, most clinical cohort studies of persons infected with HIV provide detailed individual information on behavioral risk factors, biologic markers, and treatment (5). However, cohort studies often lack the power to detect less frequent cancers and also include only selected groups of persons infected with HIV [e.g., homosexual and bisexual men (9) or hemophilic men (10)].

The Swiss HIV Cohort Study (SHCS) is a large prospective cohort that is representative of persons infected with HIV in Switzerland (11,12), with detailed follow-up information available that begins soon after diagnosis of HIV infection. Furthermore, the SHCS coverage areas largely overlap with population-based cancer registries that record comprehensive quality-checked information on cancer incidence (13). We used data from the SHCS and cancer registries to estimate excess cancer risk in persons infected with HIV and to investigate the modifying effects of HAART use and behavioral factors on cancer risk.

SUBJECTS AND METHODS

The SHCS has been enrolling persons infected with HIV from seven large hospitals in different Swiss cities (Basel, Bern, Geneva, Lausanne, Lugano, St. Gallen, and Zürich) since 1988, with some retrospective enrollment going back to 1985 *(11,12)*. The SHCS currently includes 47% of persons infected with HIV and 70% of persons with AIDS in Switzerland, as estimated from the statistics of the Federal Office of Public Health *(12)*. Any consenting person infected with HIV older than 16 years of age is eligible, and enrollment is independent of disease stage or degree of immunosuppression. Once written informed consent is obtained, detailed information (including demographic characteristics, presumed mode of HIV acquisition, last negative and first positive HIV test, and prevalent opportunistic diseases) is collected. During follow-up visits that are scheduled at 6-month intervals, individual data on selected disease diagnoses, laboratory test results, HIV/AIDS-related treatments, and death are updated. Only AIDS-defining cancers (KS, non-Hodgkin lymphoma, and, since 1993, invasive cervical cancer) *(14)* are systematically reported in the SHCS.

Nine active cancer registries, covering 56% of the Swiss population, record population-based quality-checked epidemiologic data on cancer incidence in Switzerland *(13)*. The cancer registries of Basel, Geneva, Ticino, St. Gallen and Appenzell, Vaud, and Zürich overlap directly with six of the seven regions covered by SHCS centers (all except the Bern SHCS center) (see Figure available at http://jncicancerspectrum.oupjournals.org/jnci/content/vol97/issue6). The Neuchâtel and Valais cancer registries do not directly overlap with SHCS centers, although some residents of these cantons are followed in a neighboring SHCS center (see Figure available at http://jncicancerspectrum.oupjournals.org/jnci/content/vol97/issue6). Records from the Glarus/Graubünden Cancer Registry were not available for linkage.

Swiss cancer registries vary greatly both in size and periods of cancer enrollment (Table 1). Routine indicators of data completeness and quality in the registries are good: only 1%–3% of case patients are registered on the basis of death certificates only, and the proportion of histologic verification is greater than 90% *(13)*.

Record linkage was performed using an upgraded version of an ad hoc software application that was previously designed and validated in Italy to match individuals from AIDS and cancer registries while protecting patient anonymity *(15)*. The software upgrade provided longer field lengths to allow for the common usage of concatenated surnames and multiple first names in Switzerland and was shown in a pilot study in Geneva to have a sensitivity of 99.1% (441 of 445) and 100% specificity, compared with manual verification. Personal identifiers were never made visible during linkage procedures and were not included in the output file, and therefore staff members of each registry were blinded to which persons had been linked between the SHCS and cancer registries.

Each SHCS center held its own nominal participant records. Thus, each SHCS database was independently matched with the corresponding cantonal cancer registry. Furthermore, to account for intercantonal migration and health care mobility, cross-cantonal linkages within French-speaking Switzerland (Geneva, Lausanne, Neuchâtel, and Valais) and Italian/German-speaking Switzerland (Basel, St. Gallen, Zürich, and Ticino) were also conducted.

From January 1985 through January 2003, 12 490 persons infected with HIV were enrolled in the SHCS. Persons infected with HIV were excluded from the present study (in hierarchical order) if they 1) did not report a legal residence in a canton covered by a cancer registry with which their SHCS records were linked (4076 persons infected with HIV, principally those from the Bern SHCS center), 2) had no name available in the SHCS for linkage with cancer registries (80 persons infected with HIV), or 3) were not followed in the SHCS during periods with complete data at corresponding cantonal cancer registries (1030 persons infected with HIV, principally from the Zürich SHCS center, in which no cancer registry data were available after 1996). For each person infected with HIV included in the study, the relevant time period for the calculation of person-years at risk began 3 months after the date of SHCS enrollment and ended on the date of last SHCS information, date of cancer diagnosis, or death, whichever was earliest. Person-years at risk were censored for those younger than age 16 years (13 participants) and older than age 69 years (20 participants) and if no complete cancer registry data were available in the corresponding years (see Table 1 for

Table 1. Characteristics of cancer registries and Swiss Human immunodeficiency virus Cohort Study (SHCS) centers and linked malignant cancers reported by Swiss canton of residence, 1985–2002

Canton	Cancer registry			SHCS center		Linked case patients*			
	Complete period	Population† (× 1000)	Cancer cases	Follow-up‡ period	Persons	KS	Non-Hodgkin lymphoma	Invasive cervical cancer	Other
Basel	1987–2001	429	45 450	1987–2001	831	18	22	1	23
Geneva	1970–2001	401	86 702	1985–2001	1700	49	40	1	42
Neuchâtel§	1973–2001	165	24 066	—	80	7	1	0	1
St. Gallen-Appenzell	1983–2000	510	43 986	1985–2000	517	6	12	0	6
Ticino	1996–2002	306	12 706	1996–2002	405	2	4	0	13
Valais§	1989–2001	273	17 677	—	71	3	0	0	1
Vaud	1973–2001	602	88 034	1985–2001	1310	52	44	1	24
Zürich	1980–1996	1168	81 805	1985–1996	2390	135	91	3	22
All centers		3854	400 426		7304	272	214	6	132

*Incident cases diagnosed 3 months after enrollment or later in people aged 16–69 years at or after human immunodeficiency virus infection diagnosis. KS = Kaposi sarcoma.

†From Parkin et al. *(13)*.

‡After restriction to the complete periods of corresponding cancer registries.

§Cases were linked among Neuchâtel and Valais residents enrolled in SHCS centers of neighboring cantons.

complete data periods by registry) (126 participants left-censored, 2688 participants right-censored).

Observed cancers included only incident cases reported to cancer registries during the above-defined person-years at risk. Eighty-one KSs, 25 non-Hodgkin lymphomas, two invasive cervical cancers, and eight non–AIDS-defining cancers diagnosed between 0 and 3 months from SHCS enrollment were considered prevalent cases and were not included in standardized incidence ratio (SIR) calculations. Cancers were classified according to the International Classification of Diseases for Oncology, 2nd revision (ICD-O-2) *(16)* and according to the International Classification of Diseases and Related Health Problems, 10th revision *(17)*. In situ carcinomas of the cervix (48 women) and other preneoplastic lesions (ICD-O-2 behavior codes 0–2) *(16)* were excluded from the present analysis because of incomplete reporting in cancer registries.

This study was approved by the ethics committees of the SHCS and the International Agency for Research on Cancer.

Statistical Methods

Expected numbers of incident cancers were computed from cancer registry–, sex-, age- and period-specific incidence rates *(13,18,19)*. Observed numbers of incident cancers in persons infected with HIV were compared with expected numbers by the SIR. Corresponding 95% confidence intervals (CIs) were computed using Poisson distribution *(20)*. SIRs were calculated within strata of sex, HIV exposure category (with "injecting drug or sexual contacts" being attributed to "injecting drug use"), $CD4^+$ cell count at SHCS enrollment (measured using flow cytometry), use (yes/no) of HAART (defined as prescription of at least three antiretroviral drugs, including a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor), and period before or after AIDS diagnosis *(14)*.

RESULTS

Among 7304 participants (72% male) followed for a total of 28 836 person-years, 624 incident cancers were identified (Table 1). Approximately 79% (492) of identified case patients had been diagnosed with AIDS-defining cancers, namely KS (*n* = 272), non-Hodgkin lymphoma (*n* = 214), and invasive cervical cancer (*n* = 6). An additional 132 case patients had non–AIDS-defining cancers.

Table 2 shows observed and expected numbers and corresponding SIRs for cancer sites or types with at least two cases observed. Statistically significantly elevated SIRs for persons infected with HIV compared with the general population were observed for KS (SIR = 192, 95% CI = 170 to 217), non-Hodgkin lymphoma (SIR = 76.4, 95% CI = 66.5 to 87.4), and invasive cervical cancer (SIR = 8.0, 95% CI = 2.9 to 17.4). Other statistically significantly elevated SIRs were observed for anal cancer (SIR = 33.4, 95% CI = 10.5 to 78.6); Hodgkin lymphoma (SIR = 17.3, 95% CI = 10.2 to 27.4); liver cancer (SIR = 7.0, 95% CI = 2.2 to 16.5); cancers of the lip, mouth, and pharynx (SIR = 4.1, 95% CI = 2.1 to 7.4); cancers of the trachea, lung, and bronchus (SIR = 3.2, 95% CI = 1.7 to 5.4); and nonmelanomatous skin cancer (SIR = 3.2, 95% CI = 2.2 to 4.5). Nonmelanomatous skin cancer included 26 basal cell carcinomas and five squamous cell carcinomas, and all lung cancers were histologically diagnosed as carcinomas. All non–AIDS-defining cancers combined showed a statistically significantly elevated SIR of 2.8 (95% CI = 2.3 to 3.3). The SIR for KS was much higher in women (SIR = 502, 95% CI = 239 to 927) than in men (SIR = 188, 95% CI = 166 to 212). No other relevant differences in SIRs between the sexes emerged, including SIRs for all non–AIDS-defining cancers combined (SIR = 2.9, 95% CI = 2.3 to 3.5 in men and SIR = 2.6, 95% CI = 1.7 to 3.7 in women) (Table 2).

SIRs for KS and non-Hodgkin lymphoma showed a strong inverse relationship with $CD4^+$ count at SHCS enrollment (Fig. 1). The SIRs for KS and non-Hodgkin lymphoma were 571 (95% CI = 449 to 716) and 145 (95% CI = 104 to 197), respectively, among persons infected with HIV with $CD4^+$ counts of less than 100 cells/mm^3, but 76.5 (95% CI = 52.3 to 108) and 35.8 (95% CI = 24.2 to 51.2), respectively, among persons infected with HIV with $CD4^+$ counts of more than or equal to 500 cells/mm^3. Increases in SIRs with declining $CD4^+$ counts were also seen for Hodgkin lymphoma, but they were smaller (Fig. 1). No clear association between SIR and $CD4^+$ count at enrollment was apparent for invasive cervical cancer (Fig. 1); for cancers of the lip, mouth and pharynx; for cancers of the trachea, lung, and bronchus; for nonmelanomatous skin cancer; or for all non–AIDS-defining cancers combined (Fig. 2).

When the effect of HAART use on cancer risk was investigated (Table 3), the SIR for KS was lower in users (SIR = 25.3, 95% CI = 10.8 to 50.1) than in nonusers (SIR = 239, 95% CI = 211 to 270) as was the SIR for non-Hodgkin lymphoma (SIR = 24.2, 95% CI = 15.0 to 37.1 and SIR = 99.3, 95% CI = 85.8 to 114, respectively). No invasive cervical cancer cases were observed among HAART users, and no clear differences in SIRs between HAART users and nonusers were apparent for cancers of the lip, mouth, and pharynx; anus; liver; nonmelanomatous skin cancer; or all non–AIDS-defining cancers. The SIR for Hodgkin lymphoma was higher in HAART users (SIR = 36.2, 95% CI = 16.4 to 68.9) than in nonusers (SIR = 11.4, 95% CI = 5.2 to 21.7), but the corresponding 95% confidence intervals overlapped. The difference in SIRs for Hodgkin lymphoma between HAART users and nonusers was similar in men and women (data not shown).

We repeated the analysis excluding the first 6 months of treatment from the computation of person-years of HAART use to allow a 6-month lag period for HAART to be effective. This exclusion further reduced SIRs for KS and non-Hodgkin lymphoma among HAART users to 11.4 and 16.2, respectively, but did not materially affect SIRs for other cancer sites. We also repeated the analysis excluding data from the Zürich SHCS center, which contributed data to the pre-HAART period, but not to the post-HAART period. Again, this exclusion did not materially affect results by HAART use (data not shown).

More than half of enrolled persons infected with HIV (3878 [53.1%]) never developed AIDS during the study follow-up period. However, 1415 (19.4%) were enrolled at/after AIDS diagnosis and 2011 persons infected with HIV (27.5%) were diagnosed with AIDS during follow-up. To compare the results with those of other population-based linkage studies based on AIDS diagnosis, we estimated and compared SIRs for non–AIDS-defining cancers before and after AIDS diagnosis (Table 3). For Hodgkin lymphoma, the SIR after AIDS diagnosis (SIR = 25.7, 95% CI = 9.2 to 56.2) was higher than that before diagnosis (SIR = 14.9, 95% CI = 7.7 to 26.1), although 95% confidence intervals were broad and overlapped. For all non–AIDS-defining cancers combined, SIRs before and after AIDS diagnosis were similar

Table 2. Observed (Obs) and expected (Exp) numbers of cancers, standardized incidence ratios (SIRs), and 95% confidence intervals (CIs) among people with human immunodeficiency virus infection by sex and overall in Switzerland, 1985–2002*

Cancer site or type (ICD-10)	Men		Women		All		
	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	Exp	SIR (95% CI)
Person-years since 3 months after enrollment	20 111		8725		28 836		
AIDS-defining cancers							
Kaposi sarcoma (C46)	262	188 (166 to 212)	10	502 (239 to 927)	272	1.4	192 (170 to 217)
Non-Hodgkin lymphoma (C82–C85, C96)	184	79.4 (68.4 to 91.8)	30	62.0 (41.8 to 88.6)	214	2.8	76.4 (66.5 to 87.4)
Invasive cervical cancer (C53)	—	—	6	8.0 (2.9 to 17.4)	6	0.8	8.0 (2.9 to 17.4)
Non–AIDS-defining cancers							
Lip, mouth, and pharynx† (C00–C14)	10	4.1 (1.9 to 7.5)	1	5.2 (0.0 to 29.7)	11	2.7	4.1 (2.1 to 7.4)
Stomach (C16)	1	1.0 (0.0 to 5.7)	1	6.8 (0.0 to 39.0)	2	1.1	1.7 (0.2 to 6.4)
Small intestine and colon (C17–C18)	4	2.3 (0.6 to 5.8)	0	0.0	4	2.1	1.9 (0.5 to 4.9)
Anus (C21)	4	41.8 (10.9 to 108)	1	18.5 (0.0 to 106)	5	0.1	33.4 (10.5 to 78.6)
Liver (C22)	5	7.5 (2.4 to 17.6)	0	0.0	5	0.7	7.0 (2.2 to 16.5)
Pancreas (C25)	1	1.5 (0.0 to 8.6)	1	13.1 (0.0 to 75.3)	2	0.7	2.7 (0.3 to 9.9)
Trachea, lung, and bronchus (C33, C34)	12	3.0 (1.6 to 5.3)	2	4.8 (0.5 to 17.6)	14	4.4	3.2 (1.7 to 5.4)
Skin, melanomatous (C43)	3	1.2 (0.2 to 3.5)	1	0.8 (0.0 to 4.7)	4	3.8	1.1 (0.3 to 2.8)
Skin, nonmelanomatous (C44)	26	3.6 (2.3 to 5.2)	5	2.1 (0.7 to 4.9)	31	9.7	3.2 (2.2 to 4.5)
Breast‡ (C50)	—	—	5	1.4 (0.5 to 3.4)	5	3.5	1.4 (0.5 to 3.4)
Prostate (C61)	3	1.4 (0.3 to 4.3)	—	—	3	2.1	1.4 (0.3 to 4.3)
Testis (C62)	6	1.6 (0.6 to 3.5)	—	—	6	3.8	1.6 (0.6 to 3.5)
Kidney (C64)	1	1.1 (0.0 to 6.4)	1	11.5 (0.0 to 65.8)	2	1.0	2.0 (0.2 to 7.5)
Brain (C71)	4	3.5 (0.9 to 9.1)	0	0.0	4	1.4	2.9 (0.8 to 7.6)
Thyroid (C73)	2	4.6 (0.4 to 17.0)	1	1.7 (0.0 to 9.8)	3	1.0	2.9 (0.6 to 8.7)
Hodgkin lymphoma (C81)	11	14.1 (7.0 to 25.3)	7	27.1 (10.7 to 56.2)	18	1.0	17.3 (10.2 to 27.4)
Multiple myeloma (C90)	2	6.1 (0.6 to 22.3)	0	0.0	2	0.4	5.5 (0.5 to 20.4)
Leukemias (C91–C95)	2	2.2 (0.2 to 8.1)	0	0.0	2	1.1	1.8 (0.2 to 6.7)
Non–AIDS-defining cancers§	103	2.9 (2.3 to 3.5)	29	2.6 (1.7 to 3.7)	132	47.3	2.8 (2.3 to 3.3)

*Cancers occurred since 3 months after enrollment in people aged 16–69 years. AIDS = acquired immunodeficiency syndrome.

†Includes four tongue cancers (C01–C02), four mouth cancers (C03–C06), plus one of each: lip cancer (C00); pharynx cancer (C10); and nasopharynx cancer (C11).

‡Females only.

§Includes all listed neoplasms, excluding Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer, plus three unknown primary sites, plus one of each: biliary tract (C24); nasal cavity (C30); larynx (C32); corpus uteri (C54); ovary (C56); and bladder (C67).

(SIR = 2.6, 95% CI = 2.1 to 3.2 and SIR = 3.3, 95% CI = 2.4 to 4.5, respectively).

SIRs were investigated by risk category to evaluate the influence of behavioral factors (Table 4). Thirty-two percent of persons infected with HIV were homosexual or bisexual men, 37% were intravenous drug users, and 31% belonged to other exposure categories (mostly heterosexuals, 28%). The SIR for KS was higher in homo/bisexual men (SIR = 346, 95% CI = 302 to 395) than in intravenous drug users (SIR = 33.6, 95% CI = 19.9 to 53.2), whereas heterosexuals/others had an intermediate risk (SIR = 130, 95% CI = 87.6 to 186). SIRs for non-Hodgkin lymphoma and invasive cervical cancer, where applicable, varied less across the risk categories than that of KS. SIRs for all non–AIDS-defining cancers combined were higher for intravenous drug users (SIR = 4.3, 95% CI = 3.2 to 5.7) than for homo/bisexual men (SIR = 2.6, 95% CI = 1.9 to 3.4) or heterosexuals/others (SIR = 2.0, 95% CI = 1.3 to 2.8), largely because SIRs of intravenous drug users for cancer of the trachea, lung, and bronchus (SIR = 12.6, 95% CI = 5.0 to 26.1; SIR = 1.2, 95% CI = 0.2 to 3.5; and SIR = 3.0, 95% CI = 0.8 to 7.9, respectively) and liver cancer (SIR = 50.5, 95% CI = 15.9 to 119 versus 0 in other risk categories) were higher than those in the other groups.

Information on smoking history was available for all SHCS participants followed-up after April 2000. Among all persons infected with HIV with known smoking history, 2217 (72%) were ever-smokers and 865 (28%) were never-smokers. In the subgroup of intravenous drug users, 853 (96%) were ever-smokers and 35 (4%) were never-smokers. All cancers of the lip, mouth, and pharynx (n = 3) and of the trachea, bronchus, and lung (n = 5, all lung) occurred among smokers. Among the five liver cancer cases identified, four had test results for hepatitis B virus (HBV) surface antigen, three had test results for hepatitis C virus (HCV) antibodies, and all were positive (data not shown).

DISCUSSION

In summary, we observed that persons infected with HIV who were treated with HAART had a lower risk of developing KS and non-Hodgkin lymphoma than untreated patients. No difference in risk of invasive cervical cancer or non–AIDS-related cancers was observed between HAART treated and untreated persons infected with HIV.

Association of HAART With Cancer Risks

In this study, the impact of HAART on cancer risk, based on individual treatment data, was evaluated in persons with a median follow-up of 4.8 years post-HAART. By mid-1997, 70% of SHCS participants with a history of CD4^{+} cell count less than 200 cells/mm^3 were receiving HAART (6). Decreases in KS and non-Hodgkin lymphoma risks in HAART users were evident, confirming findings from previous studies (5,21,22).

A statistically significant decline in KS, but not yet in non-Hodgkin lymphoma, had emerged in an earlier evaluation of the
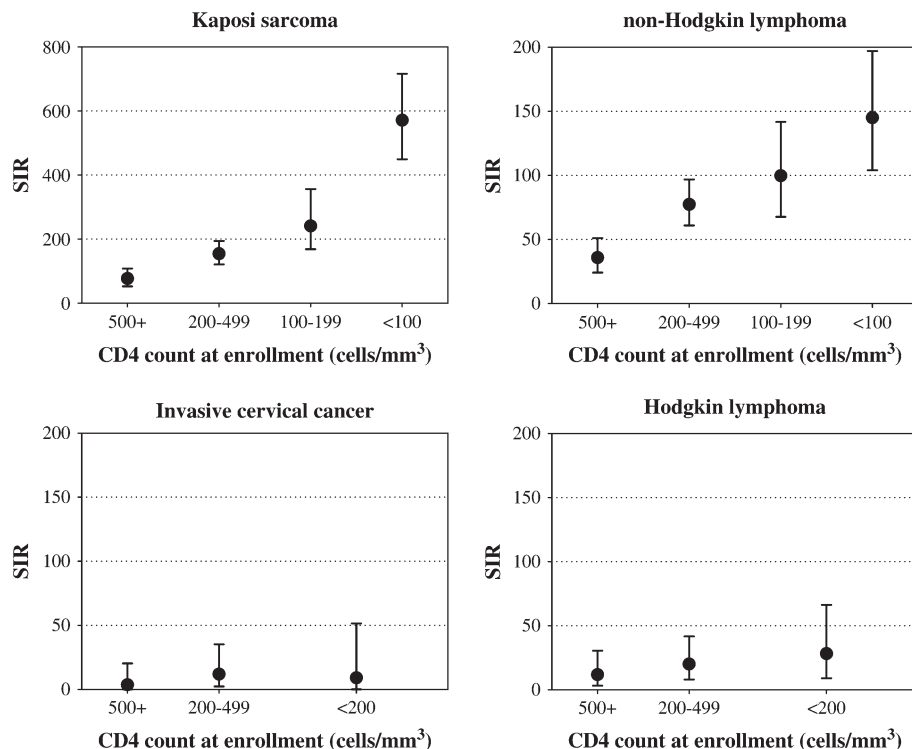
Kaposi sarcoma

non-Hodgkin lymphoma

Invasive cervical cancer

Hodgkin lymphoma

Fig. 1. Standardized incidence ratios (SIRs) and corresponding 95% confidence intervals of acquired immunodeficiency syndrome-defining cancers and Hodgkin lymphoma by CD4$^+$ cell count at enrollment, 1985–2002. Cancers occurred since 3 months after enrollment in people aged 16–69 years.

SHCS among which the 1992–1994 and 1997–1998 periods were compared *(6)*. There was no evidence from the present study that HAART was associated with a reduced SIR of cancers other than KS or non-Hodgkin lymphoma *(5)*, but rather that the SIR of certain non–AIDS-defining cancers may have actually increased in the post-HAART era. A possible explanation for this observation is that the improvement in life expectancy made possible by new antiretroviral treatment, along with

an only partial reconstitution of immune status, may allow a larger number of cancers with long latent periods to manifest clinically.

Hodgkin Lymphoma

In the present study, persons infected with HIV showed a 17-fold increased risk for Hodgkin lymphoma compared with

non-AIDS-defining cancers

Lip, mouth, and pharynx

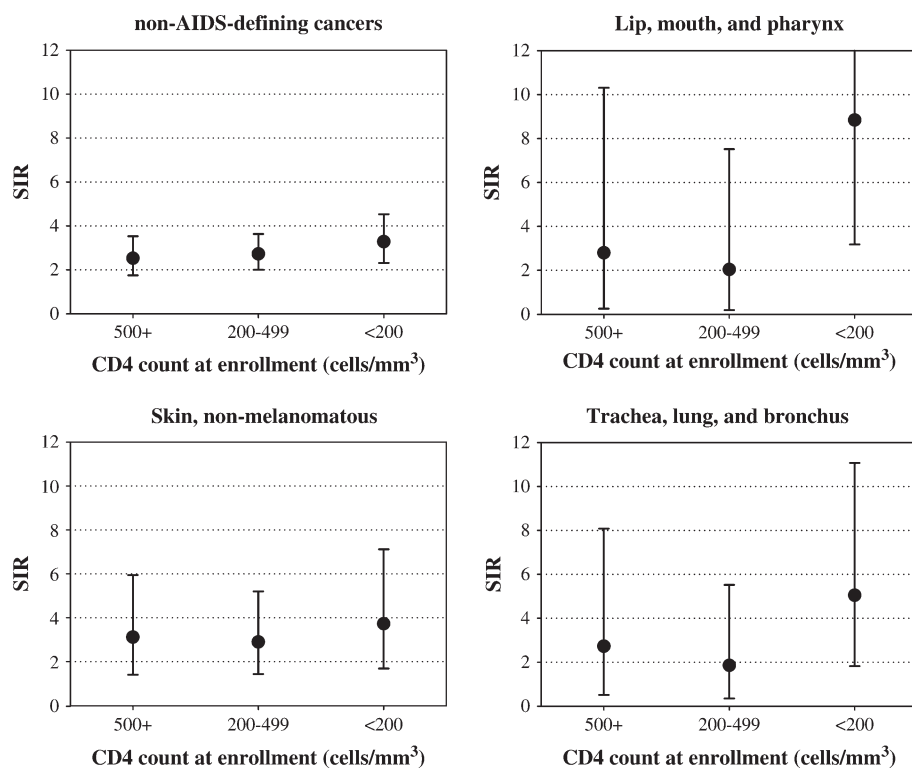## Skin, non-melanomatous

Trachea, lung, and bronchus

Fig. 2. Standardized incidence ratios (SIRs) and corresponding 95% confidence intervals of selected non–acquired immunodeficiency syndrome-defining cancers by CD4$^+$ cell count at enrollment, 1985–2002. Cancers occurred since 3 months after enrollment in people aged 16–69. The upper 95% confidence interval for lip, mouth, and pharynx cancer is 19.8.

Table 3. Observed cases (Obs) of selected cancers, standardized incidence ratios (SIRs), and corresponding 95% confidence intervals (CIs) among people with human immunodeficiency virus infection by highly active antiretroviral therapy (HAART) use and time from acquired immunodeficiency syndrome (AIDS), Switzerland, 1985–2002*

| | HAART use before cancer | | | | Time from AIDS | | | |
| | No | | Yes | | Before AIDS | | At/after AIDS | |
Cancer site or type (ICD-10)	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)
Person-years since 3 months after enrollment†		21 474		7363		22 165		6671
Kaposi's sarcoma (C46)	264	239 (211 to 270)	8	25.3 (10.8 to 50.1)	—	—	272	817 (723 to 920)
Non-Hodgkin lymphoma (C82–C85, C96)	193	99.3 (85.8 to 114)	21	24.2 (15.0 to 37.1)	—	—	214	304 (264 to 347)
Invasive cervical cancer (C53)	6	11.4 (4.1 to 25.1)	0	0.0	—	—	6	38.3 (13.8 to 83.9)
Lip, mouth, and pharynx (C00-C14)	8	5.0 (2.1 to 10.0)	3	2.8 (0.5 to 8.3)	8	4.3 (1.8 to 8.5)	3	3.8 (0.7 to 11.1)
Anus (C21)	2	22.2 (2.1 to 81.5)	3	50.4 (9.5 to 149)	4	36.1 (9.4 to 93.3)	1	25.8 (0.0 to 148)
Liver (C22)	3	7.4 (1.4 to 22.0)	2	6.4 (0.6 to 23.7)	3	6.0 (1.1 to 17.7)	2	9.5 (0.9 to 34.8)
Trachea, lung, and bronchus (C33, C34)	9	3.5 (1.6 to 6.6)	5	2.8 (0.9 to 6.5)	10	3.2 (1.5 to 6.0)	4	3.1 (0.8 to 8.0)
Skin, nonmelanomatous (C44)	14	2.7 (1.5 to 4.5)	17	3.8 (2.2 to 6.0)	25	3.6 (2.3 to 5.3)	6	2.2 (0.8 to 4.9)
Hodgkin lymphoma (C81)	9	11.4 (5.2 to 21.7)	9	36.2 (16.4 to 68.9)	12	14.9 (7.7 to 26.1)	6	25.7 (9.2 to 56.2)
Non–AIDS-defining cancers‡	76	2.6 (2.0 to 3.2)	56	3.1 (2.4 to 4.1)	90	2.6 (2.1 to 3.2)	42	3.3 (2.4 to 4.5)

*Cancers occurred since 3 months after enrollment people aged 16–69 years.

†The total does not add to 28 836 because of rounding error.

‡Includes all neoplasms but Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer.

that of the general population, which is slightly higher than in previous studies *(1,2,4)*. For the first time to our knowledge, however, the SIR for Hodgkin lymphoma showed a tendency to increase in the post-HAART era. Although the change was similar in both men and women, 95% confidence intervals on the estimates for HAART users and nonusers were broad and overlapped, and so random variation cannot be ruled out. The association between HAART and Hodgkin lymphoma incidence requires confirmation in other studies with longer follow-up after HAART.

As a consequence of changes in opposite directions, however, HAART users seem to have a similar SIR for Hodgkin lymphoma and non-Hodgkin lymphoma (although absolute numbers remain higher for non-Hodgkin lymphoma). The relationship we observed is different from past findings up to 1998, where SIRs for Hodgkin lymphoma were more than 10-fold lower than those for non-Hodgkin lymphoma *(1,4)*. A "threshold effect" of immunity on the risk of different cancers may account for the present and previous findings. Mbulaiteye et al. *(23)* reported an increased

non-Hodgkin lymphoma risk with each decline of 100 CD4+ cells/mm^3, whereas Hodgkin lymphoma risk was similar for individuals in the greater than or equal to 200, 100–199, and 50–99 CD4+ cells/mm^3 categories but much lower for individuals with less than 50 CD4+ cells/mm^3. Furthermore, although organ transplant recipients are at greatly elevated risk for non-Hodgkin lymphoma, they have little excess risk for Hodgkin lymphoma *(24)*, suggesting important differences in their relationship to immunodeficiency. Misclassification of the type of lymphoma is unlikely to account for our findings, because all Hodgkin lymphomas were histologically confirmed, and only eight cases (3%) of non-Hodgkin lymphoma were reported as lymphomas not otherwise specified.

Contribution of Smoking to Cancer Risk

Although the information on smoking history was missing for the earliest part of the cohort, it is worth noting that no lung cancers were observed in persons infected with HIV who were

Table 4. Observed cases (Obs) of selected cancers, standardized incidence ratios (SIRs), and corresponding 95% confidence intervals (CIs) among people with human immunodeficiency virus infection by exposure category, Switzerland, 1985–2002*

| | Exposure category | | | | | |
| | Homo/bisexual men | | Intravenous drug users | | Heterosexual/other† | |
Cancer site or type (ICD-10)	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)
Person-years since 3 months after enrollment‡		9090		11 641		8106
Kaposi sarcoma (C46)	224	346 (302 to 395)	18	33.6 (19.9 to 53.2)	30	130 (87.6 to 186)
Non-Hodgkin lymphoma (C82–C85, C96)	111	93.7 (77.0 to 113)	56	62.8 (47.4 to 81.5)	47	64.9 (47.7 to 86.4)
Invasive cervical cancer (C53)	—	—	4	10.9 (2.8 to 28.2)	2	5.2 (0.5 to 19.0)
Lip, mouth, and pharynx (C00–C14)	3	2.0 (0.4 to 5.8)	6	13.7 (4.9 to 30.1)	2	2.9 (0.3 to 10.5)
Anus (C21)	4	68.0 (17.7 to 176)	1	27.4 (0.0 to 157)	0	0.0
Liver (C22)	0	0.0	5	50.5 (15.9 to 119)	0	0.0
Trachea, lung, and bronchus (C33, C34)	3	1.2 (0.2 to 3.5)	7	12.6 (5.0 to 26.1)	4	3.0 (0.8 to 7.9)
Skin, nonmelanomatous (C44)	19	4.6 (2.8 to 7.2)	9	4.2 (1.9 to 8.0)	3	0.9 (0.2 to 2.6)
Hodgkin lymphoma (C81)	6	17.7 (6.4 to 38.8)	6	14.0 (5.0 to 30.6)	6	22.2 (8.0 to 48.6)
Non–AIDS-defining cancers§	53	2.6 (1.9 to 3.4)	49	4.3 (3.2 to 5.7)	30	2.0 (1.3 to 2.8)

*Cancers occurred since 3 months after enrollment in people aged 16–69 years. AIDS = acquired immunodeficiency syndrome.

†"Unknown" exposure category included (324 person-years).

‡The total does not add to 28 836 because of rounding error.

§Includes all neoplasms but Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer.

nonsmokers, and excess risks were insensitive to CD4+ counts. Thus, a threefold excess risk of cancers of the trachea, lung, and bronchus in all persons infected with HIV, consistent with previous studies *(1–5,25)*, seems to be directly attributable to high smoking levels of persons infected with HIV *(26)*, particularly intravenous drug users *(27)*. The fact that all lung cancers were histologically diagnosed carcinomas excludes, however, misclassification with masses of non-neoplastic origin or non-Hodgkin lymphoma in our study. Cancers of the lip, mouth, and pharynx showed a risk pattern similar to that of cancer of the lung, with a predominance among intravenous drug users and a lack of case patients among nonsmokers.

We observed a high prevalence of smoking in the SHCS (72% overall, 96% in intravenous drug users). This observation illustrates the great importance, especially after the introduction of HAART, of planning active smoking cessation programs for persons infected with HIV *(7)*.

Human Papillomavirus–Related Cancers

Immunity is important for the clearance of human papillomavirus (HPV) infection and of preneoplastic lesions of the anogenital tract *(28)*, and our present study confirmed the fact that persons infected with HIV are at excess risk for HPV-related cancers (i.e., cervical and anal cancer). The excess risk of invasive cervical cancer found in women in the SHCS (SIR = 8.0) confirms reports from record linkage studies from the United States and Italy *(1,4)*. As reported previously *(1,2,4)*, the SIR for anal cancer (31.9) was much more elevated than that of invasive cervical cancer, but anal cancer was nearly restricted to homosexual and bisexual men (four of five anal cancer cases). Increased exposure to HPV through anal intercourse may therefore contribute substantially, along with impaired immunity, to the strength of the observed association. SIRs for invasive cervical cancer and anal cancer were not clearly affected by the CD4+ count or HAART use.

At least two additional types of cancer may be associated with HPV. Mucosal HPV types are associated with a fraction of cancers of the mouth and pharynx *(29)*. HPV may thus contribute, along with smoking, to the fourfold increased risk of cancer of the lip, mouth, and pharynx observed in the SHCS. Finally, nonmelanomatous skin cancer, which is associated with cutaneous HPV types *(30)*, was found to be increased by threefold in the SHCS. This increase is in agreement with the SIR reported in Australia (4.2) *(2)* and Scotland (2.8) *(3)*, and slightly higher than the SIR from Italy (1.5) *(4)*. Although the SIR is statistically significant, the excess of this tumor in persons infected with HIV is still approximately 10-fold less than that among organ transplant recipients *(24)*. Furthermore, the squamous/basal cell cancer ratio in this study was low (5/26), at variance with what is reported among organ transplant recipients *(30)*. Misclassification with KS appears unlikely because all skin cancers in our study were histologically confirmed.

Liver Cancer in Persons Infected With HIV

Liver cancer is etiologically linked with infection with HBV and HCV, but the influence of immune status on the development of chronic hepatitis, cirrhosis, and hepatocellular carcinoma is not well understood. No clear excess of liver cancer in people with HIV or AIDS emerged in early studies *(31)*. The sevenfold excess risk of liver cancer in the SHCS is consistent with an eightfold risk identified in people with AIDS in the United States *(1)* but greater than those found in Italy *(4)* (1.9) and Australia *(2)* (2.7).

Although the excess of hepatocellular carcinoma in Swiss persons infected with HIV was primarily due to co-infection with HBV and/or HCV in intravenous drug users, it remains difficult to disentangle the direct interaction of HIV and HBV/HCV from the effect of their common transmission route. Nevertheless, co-infection with HIV and HCV or HBV, respectively, led to higher mortality from liver cancer than did HCV or HBV infection alone in a study of British hemophilic men and boys *(10)* and of homosexual men in the United States *(9)*.

Study Strengths and Limitations

The SHCS has many strengths, including a large cohort size, length, and completeness of follow-up and availability of information, at least for a proportion of persons infected with HIV, on cancer risk factors. Approximately half of persons infected with HIV as well as the majority of AIDS patients in Switzerland have been enrolled in the SHCS, and both sexes and different risk categories are well represented. Another major strength of the present methodology was the access to follow-up of persons infected with HIV soon after HIV diagnosis, many of whom (53%) never developed AIDS. To identify cancers influenced by HIV-induced immunosuppression, most previous studies compared cancer risks in persons with AIDS before and after AIDS *(1)*, as well as by CD4+ counts at AIDS diagnosis *(4,8,32)* but could not evaluate risks in persons infected with HIV who never developed AIDS before cancer or death.

This study also has some limitations. Sixty KS, 34 non-Hodgkin lymphoma, five invasive cervical cancer, and four Hodgkin lymphoma cases recorded in the SHCS during the relevant person-years at risk could not be identified in corresponding cancer registries and are not included in SIR calculations. Although these missed incident cases may simply have turned out not to be malignancies on histologic confirmation, they may also have resulted from undermatching due to inaccuracies in personal identifiers and self-reported legal residence in the SHCS. Conversely, some KS cases may not have been biopsied, resulting in under-reporting to cancer registries. Both undermatching and under-reporting would result in an underestimation of SIRs. Although the inverse problem of overmatching may also have occurred, resulting in an overestimation of SIRs, we expect it to have been minimal, given the high specificity of the linkage procedure *(15)*. The potential for overestimation of person-years under surveillance and ascertainment bias associated with AIDS diagnosis (inherent in previous linkage studies using AIDS registries) should also be small, given that all persons infected with HIV were under close active follow-up and that the majority were not diagnosed with AIDS during this period.

In conclusion, HAART treatment may prevent excess risk of KS and non-Hodgkin lymphoma, but not that of Hodgkin lymphoma or other non–AIDS-defining cancers. Focusing on ways to encourage persons infected with HIV to quit smoking would be effective in reducing lung cancer in these persons.

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