

## Articles

## Spectrum of AIDS-associated malignant disorders

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## Summary

**Background** To clarify which types of cancer result from AIDS, we compared the cancer experiences of people with AIDS with those of the general population by matching population-based cancer and AIDS registries in the USA and Puerto Rico.

**Methods** We used a probabilistic matching algorithm to compare names, birth dates, and, where available, social-security numbers of 98 336 people with AIDS and 1 125 098 people with cancer aged less than 70 years. We defined AIDS-related cancers as those with both significantly raised incidence post-AIDS and increasing prevalence from 5 years pre-AIDS to 2 years post-AIDS.

**Findings** Among people with AIDS, we found 7028 cases of Kaposi's sarcoma (KS), 1793 of non-Hodgkin lymphoma (NHL), and 712 other cases of histologically defined cancer. Incidence rates among people with AIDS were increased 310-fold for KS, 113-fold for NHL, and 1.9-fold (95% CI 1.5–2.3) for other cancers. Of 38 malignant disorders other than KS and NHL, only angiosarcoma (36.7-fold), Hodgkin's disease (7.6-fold), multiple myeloma (4.5-fold), brain cancer (3.5-fold), and seminoma (2.9-fold) were raised and increasing significantly ( $p < 0.02$ ) from the pre-AIDS to the post-AIDS period.

**Interpretation** Interpretation is complicated by screening and shared risk factors, such as sexual behaviour and cigarette smoking. However, our data indicate that AIDS leads to a significantly increased risk of Hodgkin's disease, multiple myeloma, brain cancer, and seminoma. Immunological failure to control herpes or other viral infections may contribute to these malignant diseases.

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## Introduction

Cancer risk is increased with most types of immune deficiency, including congenital disorders and iatrogenic treatments to prevent allograft rejection.<sup>1</sup> With AIDS, cancer risk is extraordinarily high and has an unusual spectrum.<sup>1,2</sup> An understanding of this spectrum may clarify the interplay between immunity, viruses, and other carcinogenic agents, and indirect carcinogenic mechanisms, including regulators of mitosis and growth. Kaposi's sarcoma (KS) and high-grade B-cell non-Hodgkin lymphoma (NHL) are the prototypical AIDS-defining malignant diseases, with 2419 and 1030 cases, respectively, reported to the Centers for Disease Control and Prevention during 1996.<sup>3</sup> However, many other neoplasms have been reported among people with AIDS. Causal relations between AIDS and these other cancers have not been defined because of potential confounding by sexual and other lifestyle variables, and because of ascertainment bias from the intensive diagnostic scrutiny of people with AIDS. To clarify these issues we established the AIDS-Cancer Match Registry, and developed methods to examine the relation between AIDS—defined as the initial life-threatening opportunistic illness—and the prevalence and incidence of 38 histologically defined malignant disorders reported to population-based cancer registries in the USA and Puerto Rico.

## Methods

*Matching and linkage of AIDS and cancer data*

The National Cancer Institute collaborated with the population-based cancer registries and AIDS registries in Puerto Rico and in seven regions in the USA (New Jersey, Florida, Atlanta, San Francisco, Los Angeles, San Diego, and Sacramento). Records were linked by computer with a probabilistic algorithm that matched social-security numbers in those registries in which they were available (San Francisco and Los Angeles).<sup>4</sup> For the other regions, the matching algorithm incorporated two critical fields (last name and date of birth) plus equivalents of first name (eg, William and Bill) as defined by an automated first-name thesaurus. A one-character difference (such as a deletion or substitution) in one critical field was allowed if the other critical field had an identical match. For efficiency, matching was limited to patients with AIDS and cancer aged under 70 years.

*Histopathological review and detection of Epstein-Barr virus*

To assess the chance that a spuriously high risk of Hodgkin's disease with AIDS could result from misdiagnosis of AIDS-NHL cases, we obtained formalin-fixed paraffin-embedded tumour blocks (or unstained sections) from 20 patients with AIDS-associated lymphoma (two patients with NHL and all 18 available patients with Hodgkin's disease) in one population-based registry for histopathological review. 4  $\mu$ m sections were cut and stained with haematoxylin and eosin. We made diagnoses

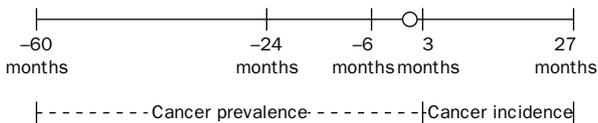


Figure 1: **87 months during which cancer risk was assessed among people with AIDS and compared with general US population**

Population-based AIDS and cancer registries were linked to identify people with AIDS who had ever had cancer reported to registry. Month of initial AIDS-defining disease was defined as month +1 (circle). 2-year cancer-incidence rates were calculated for cohort of people with AIDS who survived at least 3 months after their AIDS-defining disease (months +4 to +27). Prevalence of cancer among people with AIDS was calculated for three time periods—early pre-AIDS (–60 to –25), later pre-AIDS (–24 to –7), and at AIDS (–6 to +3). Cancer prevalence and incidence rates among people with AIDS were compared to those expected to have occurred among people of same age, race, and sex distribution as people with AIDS.<sup>7</sup>

using standard histopathological criteria. The RNA in-situ hybridisation technique was used to detect the Epstein-Barr virus early-RNA-1 (EBER1) gene product in Hodgkin's disease tissue.<sup>3</sup> Briefly, formalin-fixed tissue sections were hybridised with the EBER1 riboprobe by means of a colorimetric detection system. We interpreted sections showing hybridisation signal within the majority of Reed-Sternberg cells as positive for Epstein-Barr virus.

#### Coding, file format, and analysis

Uniform coding of 38 histologically defined malignant disorders (available upon request) was done by use of the International Classification of Diseases for Oncology.<sup>6</sup> Owing to the inconsistency in the coding of race in the population data (AIDS registries, cancer registries, and a US census), this study was limited to two race-ethnic groups—whites (including all Hispanic people) and blacks. A person with AIDS was deemed to be at risk of an AIDS-related malignant disease from 60 months before to 27 months after the first condition that met the 1987 AIDS surveillance definition of the US Centers for Disease Control and Prevention (defined as month +1; figure 1). Some cases of KS and NHL that were reported to cancer surveillance occurred before the earliest condition was reported to AIDS surveillance. For this study, all cases of KS were deemed to be AIDS-defining. For NHL, cases that occurred up to 3 years before the initial AIDS-registry report were regarded as AIDS-defining, but the 11 cases that occurred 37–60 months before the onset of AIDS were not. AIDS onset (month +1) was backdated more than 6 months for 329 patients with KS and 87 with NHL.

Period prevalence is the frequency of a condition that

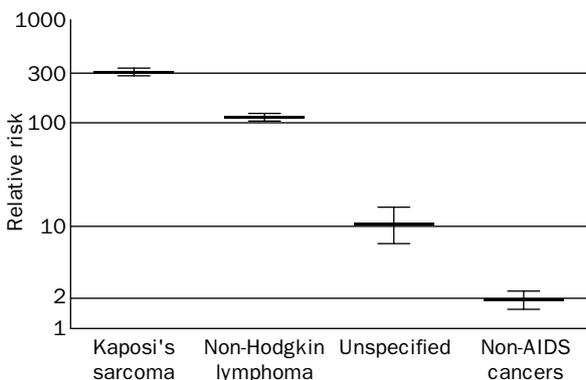


Figure 2: **Relative risk ( $\log_{10}$  scale) and 95% CIs of post-AIDS cancer incidence**

Data for two prototypic AIDS-associated malignant disorders—Kaposi's sarcoma ( $n=1827$ ) and non-Hodgkin lymphoma ( $n=517$ )—for malignant disorders with no specific histology recorded by cancer registries ( $n=27$ ), and for histologically specified malignant diseases considered not related to AIDS ( $n=108$ ). Risk of non-AIDS cancers was significantly increased 1.9-fold (95% CI 1.5–2.3).

occurred previously among people who survived to a selected time point (eg, month +1). We calculated the prevalence of cancer among people with AIDS for three time periods—early pre-AIDS (month –60 to –25), later pre-AIDS (months –24 to –7), and at AIDS (months –6 to +3). Cancer period prevalence among people with AIDS was compared with the period prevalence of cancer (as estimated by the Surveillance, Epidemiology, and End Results [SEER] registry network of the National Cancer Institute)<sup>7</sup> during 1986 through to 1990 that was expected to have occurred among people of the same age, race, and sex distribution as the people with AIDS. In contrast to prevalence, incidence is calculated prospectively and is less affected by survivorship. We calculated 2-year cancer incidence rates for the cohort of people with AIDS who survived for at least 3 months after their AIDS-defining disease (months +4 to +27) and compared these rates with the incidence of cancer<sup>7</sup> during the period 1985–89 that was expected to have occurred among people of the same age, race, and sex distribution as the people with AIDS. For both incidence and prevalence, observed (O) cases among people with AIDS were compared with expected (E) cases in the population matched for age, sex, and race; we used the O/E ratio to estimate relative risk (RR) and Poisson assumptions to calculate exact 95% CIs. The significance of changes in RR over time were estimated as p-for-trend values based on a score test of  $\beta=0$  in a Poisson regression model with expectation (E) $\exp(\beta t)$ , where E is the expected cancer count based on prevalence or incidence rates in the general population, and time  $t$  (–42.5, –15.5, or 15.5) represents the midpoints of the early pre-AIDS, later pre-AIDS, and post-AIDS periods. The AIDS period was excluded from this trend analysis.

#### Results

The AIDS-Cancer Match Registry compared the records of 98 336 people with AIDS with the records of 1 125 098 people with cancer. For the cohort analysis, there were 40 733 post-AIDS person-years at risk, including 26 398 person-years (65%) for white or Hispanic homosexual men, 3336 (8%) for black homosexual men, 7386 (18%) for other males, and 3612 (9%) for females.

#### KS and NHL

Using the pre-epidemic (1975–79) US population as the reference group, we calculated the RR for KS and NHL to be 100 000 times and 280 times higher, respectively, for patients with AIDS.<sup>8</sup> Because the contemporaneous (1985–89) US reference population included people with AIDS-related cancers, more conservative risk estimates resulted: 310-fold for KS and 113-fold for NHL (figure 2). 86 tumours lacking a specific histology were linked to people with AIDS (RR 10.2), but we excluded these from further analysis owing to the possibility that they were NHL or KS.

#### Risk of other cancers among people with AIDS

We classified cancers other than KS and NHL as AIDS-related only if there was a significantly increased post-AIDS incidence and a significantly rising trend from the early pre-AIDS period to the post-AIDS period, excluding the AIDS period, which could be biased by ascertainment. The table provides the profile of risks for most types of cancer. Other than KS and NHL, 712 tumours with histology were matched to AIDS cases. The incidence rate of these “non-AIDS” cancers was 1.9-fold higher than in the general population (RR 1.9 [95% CI 1.5–2.3]). Furthermore, the RR rose significantly from the early pre-AIDS period to the post-AIDS period (p for trend <0.0001).

Cancer type or site	Cancer cases observed/expected during time interval				p for trend†
	25–60 months pre-AIDS	7–24 months pre-AIDS	AIDS period	4–27 months post-AIDS	
Kaposi's sarcoma	NA	NA	5181/5.16	1827/5.88*	NA
Non-Hodgkin lymphoma	NA	NA	1276/3.93	517/4.42*	NA
Non-AIDS cancers	166/171.85	162/111.85	276/57.33	108/56.64*	<10 <sup>-4</sup>
Oropharynx	13/9.12	8/6.49	5/3.39	4/3.13	0.76
Larynx	8/4.60	4/3.06	2/1.51	2/1.25	0.74
Thyroid	3/6.38	2/3.20	3/1.29	3/1.24	0.09
Stomach	2/1.26	3/1.27	3/1.09	1/1.27	0.74
Colon	5/11.10	3/8.13	2/4.22	2/3.86	0.99
Bladder	4/12.10	3/7.60	4/3.38	0/2.97	0.64
Kidney and other urinary	5/5.86	3/4.12	4/2.10	5/2.03	0.21
Prostate	8/11.95	3/10.61	7/5.24	2/4.22	0.30
Female breast	11/9.47	5/6.18	0/2.48	1/1.80	0.36
Hepatocellular	0/0.09	1/0.08	7/0.14	0/0.32	0.78
Angiosarcoma	0/0.18	0/0.09	3/0.05	2/0.05*	0.02
Soft-tissue sarcoma	0/1.04	0/0.78	6/0.42	3/0.42*	0.01
Bone and other sarcomas	1/3.24	1/1.89	1/0.79	1/0.79	0.36
Hodgkin's disease	16/8.35	39/4.03	72/1.70	13/1.70*	<10 <sup>-4</sup>
Leukaemia, lymphoid	3/2.01	4/1.45	10/0.78	1/0.74	0.72
Leukaemia, myeloid	8/1.76	2/1.55	10/0.90	3/1.02	0.22
Leukaemia, other	0/0.69	2/0.52	7/0.26	4/0.36*	0.01
Multiple myeloma	0/1.69	2/1.50	11/0.76	3/0.67*	0.015
Brain	0/3.86	2/3.14	13/1.75	7/1.99*	0.006
Seminoma or germinoma	6/9.40	10/5.00	15/2.04	6/2.09*	0.003
Other male germ cell	5/6.42	1/2.97	1/1.18	2/1.30	0.85
Anal	7/0.46	13/0.37	9/0.21	6/0.19*	0.085
Cervix, in situ	14/20.32	14/8.57	3/3.08	4/2.41	0.01
Cervix, invasive	12/2.22	4/1.13	2/0.45	1/0.35	0.37
Malignant melanoma	19/17.22	13/10.04	9/4.74	5/4.53	0.80
Other skin	1/1.83	0/0.93	5/0.42	2/0.37	0.12
Squamous-cell carcinoma, unusual sites	3/1.30	3/0.87	5/0.45	3/0.44*	0.22
Lung, adenocarcinoma	2/2.59	2/2.85	16/2.42	7/2.81*	0.13
Lung, other	5/5.44	11/5.77	26/5.19	7/5.93	0.54
Adenocarcinoma, unusual sites	3/7.57	1/6.17	7/3.44	6/3.51	0.08
Miscellaneous	1/2.91	2/1.60	4/0.89	2/0.97	0.11
Unspecified	8/3.10	7/2.32	44/1.97	27/2.64*	0.004

\*Post-AIDS relative risks (95% CI): Kaposi's sarcoma 310.2 (291.6–329.5); non-Hodgkin lymphoma 112.9 (103.6–123.4); non-AIDS cancers 1.9 (1.5–2.3); angiosarcoma 36.7 (4.4–132.5); soft-tissue sarcoma 7.2 (1.5–21.0); Hodgkin's disease 7.6 (4.1–13.1); leukaemia, other 11.0 (3.0–28.3); multiple myeloma 4.5 (0.9–13.2); brain 3.5 (1.4–7.2); seminoma or germinoma 2.9 (1.1–6.3); anal 31.7 (11.6–69.2); squamous-cell carcinoma, unusual sites 6.8 (1.4–19.8); lung, adenocarcinoma 2.5 (1.0–5.1); unspecified 10.2 (6.7–14.9). †p for trend test for change in relative risk across time intervals, excluding AIDS period. NA=not applicable.

#### Observed cases, expected cases, and relative risks of malignant diseases among people with AIDS

The increased risk was not randomly distributed among cancer types. Most of the common malignant disorders were not associated with AIDS; these disorders included cancers of the oropharynx (RR 1.3), larynx (1.6), thyroid (2.4), stomach (0.8), colon (0.5), kidney (2.5), and prostate (0.5). No post-AIDS-incidence cancer cases were noted for the nasopharynx, oesophagus, pancreas, bladder, penis, uterine corpus, or ovary; and only one case of breast cancer (RR 0.6) occurred among women with AIDS. Hepatocellular carcinoma prevalence was very high (seven cases, RR 49.3) during the AIDS period, but there were no post-AIDS cases.

Various tumour types were associated with AIDS. In order of relative risk in the post-AIDS period, they were angiosarcoma (RR 36.7); anal cancer (31.7); leukaemias other than lymphoid and myeloid (11.0); Hodgkin's disease (7.6); leiomyosarcoma and other soft-tissue sarcomas (7.2); multiple myeloma and malignant plasmacytoma (4.5); primary brain cancers (3.5); seminoma or malignant germinoma (2.9); and lung adenocarcinomas (2.5). Some of these could have trivial

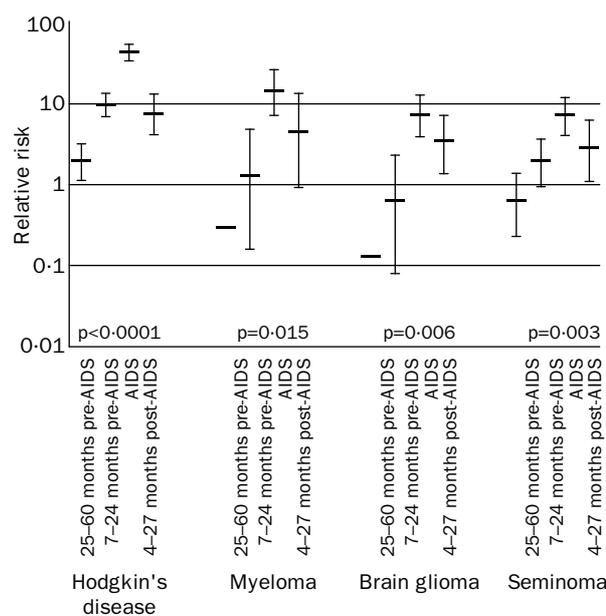


Figure 3: Relative risks ( $\log_{10}$  scale) of four malignant diseases for which incidence rates were increased post-AIDS

Multiple myeloma included malignant plasmacytoma, malignant gliomas included astrocytomas of brain, and seminoma included malignant germinoma of testis and mediastinum. All these tumours also had a significantly increasing risk across three time periods (early pre-AIDS [months –25 to –60], later pre-AIDS [–7 to –24], and post-AIDS [+4 to +27]) that are associated with worsening immunodeficiency among people with HIV-1 infection. We found no prevalent cases of myeloma or brain glioma (compared with 1.69 and 3.86, respectively, expected) 25–60 months before AIDS; 0.5 observed cases was assumed for these two tumours 25–60 months before AIDS.

explanations—angiosarcoma, for example, resembles KS, and some or all of the five cases linked to people with AIDS could have been misdiagnosed. Similarly, only one of the nine soft-tissue sarcomas among people with AIDS was a leiomyosarcoma of the retroperitoneum; the other eight were histologically unspecified sarcomas, including four skin tumours that may have been KS. People with AIDS were not at increased risk of bone or other sarcomas (RR 1.3).

#### Hodgkin's disease

The risk of Hodgkin's disease was 7.6 times higher after the onset of AIDS, and the RR of Hodgkin's disease increased from early pre-AIDS to post-AIDS (figure 3; p for trend <0.0001). When reviewed by pathologists, two of two AIDS-NHL cases were verified as correct, as were 16 of 18 cases of Hodgkin's disease, including ten mixed-cellularity subtype, three nodular-sclerosis subtype (two with lymphocyte depletion), two lymphocyte-depletion subtype, and one specimen that was too small for subtyping. We found no malignant disease in slides from two of the patients reported to have Hodgkin's disease. 13 (87%) of the 15 Hodgkin's disease tissues that were satisfactory for analysis were positive for Epstein-Barr-virus RNA (EBER1).

#### Leukaemia and myeloma

The incidence rates of lymphoid and myeloid leukaemia were not significantly increased in the post-AIDS period (RR 1.4 and 3.0, respectively). However, cases of leukaemia that were not coded as lymphoid or myeloid increased from zero early pre-AIDS to 11-fold (95% CI 3.0–28.3) post-AIDS (p for trend=0.01). The 13

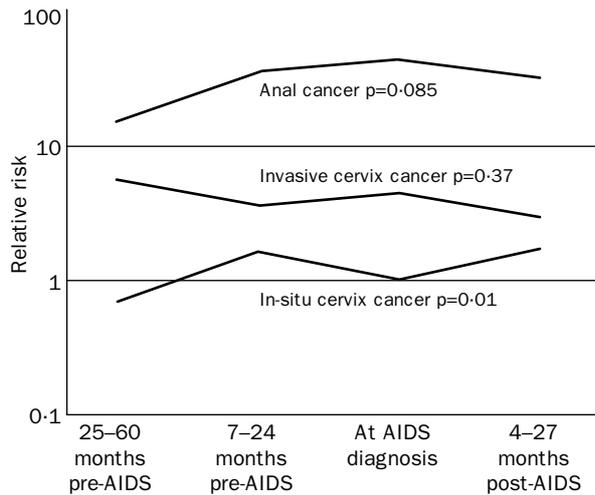


Figure 4: **Relative risks (log<sub>10</sub> scale) for people with AIDS of three closely related anogenital malignant disorders**

Anal cancer risk was high but only doubled from early pre-AIDS (months -25 to -60) to later pre-AIDS (-7 to -24), and post-AIDS (+4 to +27) periods. In contrast to anal cancer, high risk of invasive and low risk of in-situ cervical cancer in early pre-AIDS period suggests infrequent cytological screening. Changes over time, increased risk of in-situ cancer, and slight decrease of invasive cancer, suggest increasing frequency of screening but no large increase in cervical-cancer risk due to AIDS.

miscellaneous leukaemia cases among people with AIDS included two of hairy-cell leukaemia, two of acute myelofibrosis, one of acute monocytic leukaemia, and eight of unspecified leukaemia. Some of these cases might possibly be leukaemoid transformations of AIDS-related NHL.

People with AIDS did seem to be at increased risk of multiple myeloma, which had a marginally higher post-AIDS incidence (RR 4.5 [95% CI 0.9–13.2]). The risk ratio of multiple myeloma increased significantly—from zero early pre-AIDS, to 1.3-fold during later pre-AIDS, to 4.5-fold post-AIDS (figure 3; *p* for trend=0.015). Ten of the 16 cases of multiple myeloma among people with AIDS occurred in homosexual men.

#### Brain cancer

We found a significantly increased incidence of brain cancer among people with AIDS (RR 3.5 [95% CI 1.4–7.2]). The brain cancers also had increasing prevalence from zero early pre-AIDS, to two cases (0.6) later pre-AIDS, to seven cases (3.5) post-AIDS (*p* for trend=0.006). Although the histological codes for these brain cancers among people with AIDS were quite specific—with 20 cases of malignant glioma or astrocytoma, and one case each of oligodendroblastoma and primitive neuroectodermal tumour—these tissues have not been independently verified to exclude misdiagnosis of other central-nervous-system diseases that are common with AIDS.

#### Testicular cancer

We found a significantly increased risk of testicular or mediastinal seminoma among people with AIDS (post-AIDS RR 2.9). The risk ratio of seminoma increased from early pre-AIDS to post-AIDS (*p* for trend=0.003). The RR of other male-germ cell tumours was not increased in post-AIDS incidence (1.5), nor over time (*p* for trend=0.85).

#### Anal and cervical cancer

The risk of anal cancer post-AIDS was very high (RR 31.7 [11.6–69.2]), as we reported previously;<sup>9</sup> however, it also was high in the early pre-AIDS period (15.1) and only doubled from then to the post-AIDS period (*p* for trend=0.085). The risk of in-situ cervical carcinoma among women with AIDS was low in the early pre-AIDS interval (RR 0.7), but increased over time to a figure slightly above the incidence in the general population (post-AIDS RR 1.7, *p* for trend=0.01; figure 4). A different pattern occurred in the risk of invasive cancer of the cervix, with the highest risk in the early pre-AIDS period (RR 5.4); the risk then decreased slightly as AIDS approached and passed (*p* for trend=0.37). The risk of invasive cervical cancer was higher—though not significantly—in the post-AIDS period (RR 2.9 [0.7–16.0]).

#### Skin and other epithelial cancers

The risk of non-melanoma (basal-cell and squamous-cell) skin cancer was raised but not significantly (RR 5.4 [0.7–19.5]) post-AIDS, and we found no evidence of an increased risk of malignant melanoma (1.1). The risk of squamous-cell cancer at various unusual sites (four tumours of the conjunctiva;<sup>10</sup> four at unknown sites; two each of the nasal cavity, maxillary sinus, lip, and vulva; one of the trachea) was significantly increased post-AIDS (RR 6.8 [1.4–19.8]), but the RR did not increase significantly over time (*p* for trend=0.22).

The incidence of adenocarcinoma of the lung was significantly increased (RR 2.5 [1.0–5.1]). However, we recorded no increase for other histological types of lung cancer (RR 1.2), and the RR did not increase from pre-AIDS to post-AIDS, for either adenocarcinomas (*p* for trend=0.13) or lung cancers of other histological types (*p* for trend=0.54). The incidence of adenocarcinoma at various unusual sites was not significantly increased (RR 1.7), and the increase in RR from pre-AIDS to post-AIDS was weak (*p* for trend=0.08). Miscellaneous neoplasms in people with AIDS did not increase significantly in incidence (2.1) nor in time (*p* for trend=0.11).

#### Discussion

This study expands the known spectrum of AIDS-related malignant disorders and also shows that most cancers are not related to immunodeficiency. The experiences of patients with AIDS and other immunodeficiencies help elucidate the cause of some tumours. Nearly all immunodeficiency states have in common an extraordinary risk of NHL that roughly parallels the intensity of immune stimulation and the severity of immune deficiency. For kidney-transplant recipients, NHL risk is increased most within the first year after allografting when antirejection therapy is most intensive.<sup>1</sup> Acute graft-versus-host disease and intensive immunosuppressive therapy during the first year after a bone-marrow transplant are associated with a greatly increased risk of NHL.<sup>1</sup> These transplant-associated lymphomas seem to be driven by infection with Epstein-Barr virus.

With AIDS, the risk of NHL increases with longer survival.<sup>2,8</sup> Epstein-Barr virus is linked to roughly half of all cases of systemic AIDS-NHL, and to nearly all cases of AIDS-associated and non-AIDS-associated NHL of the brain.<sup>2</sup> Epstein-Barr virus genome and expression has

also been found in all seven smooth-muscle tumours studied from children with AIDS, including monoclonal Epstein-Barr virus episomes in two tumours,<sup>2,11</sup> and in the tumour of a post-transplant patient.<sup>12</sup> However, the absence of Epstein-Barr virus in seven tumours from children without AIDS and in two adults with soft-tissue sarcomas<sup>11,13</sup> shows that Epstein-Barr virus is not necessary for formation of these tumours.

The risk of Hodgkin's disease may be slightly raised with congenital immunodeficiency, but does not seem to be higher in patients with transplants.<sup>1</sup> Nonetheless, we found that the risk of Hodgkin's disease among people with AIDS was increased roughly eight-fold—a rise similar to that recorded in other studies.<sup>2</sup> We found that Hodgkin's disease risk was not significantly increased more than 2 years before the AIDS-defining disease, making confounding unlikely. Moreover, our finding that most (16 [89%] of 18) of the Hodgkin's disease diagnoses were correct corroborates a large clinical study with pathologically verified AIDS-associated Hodgkin's disease.<sup>2</sup> Our population-based sample confirmed the presence and expression of Epstein-Barr virus in the vast majority of AIDS-Hodgkin's tumour tissue. In the general, non-AIDS population, Epstein-Barr-virus expression is found in about 25% of cases,<sup>14</sup> and there is a seven-fold to 14-fold increase in the risk of Hodgkin's disease with raised Epstein-Barr virus antibodies.<sup>15</sup>

The risk of multiple myeloma is marginally increased after non-AIDS KS,<sup>16,17</sup> but none of the previous cancer-registry studies, and only one cohort study of HIV-1-infected homosexual men, reported a myeloma excess.<sup>2,18</sup> Epstein-Barr virus has been linked to multiple myeloma among transplant recipients and, in a few cases, among people with AIDS.<sup>2</sup> In 1996, Rettig and colleagues reported that human herpesvirus 8—a gamma herpesvirus with substantial aminoacid homology to Epstein-Barr virus<sup>19</sup>—could be detected in bone-marrow dendritic cells, but not in malignant plasma cells, of patients with multiple myeloma.<sup>20</sup> Human herpesvirus 8 encodes a functional homologue of interleukin-6<sup>21</sup> that may serve as a paracrine stimulant of myeloma cells.<sup>20,22</sup> However, the association of this virus with multiple myeloma has been difficult to replicate.<sup>23</sup>

Testicular and brain cancers have not been clearly linked to immunodeficiency. Lyter and colleagues<sup>24</sup> reported a significant excess of seminoma among HIV-1-infected homosexual men, but this report was based on three cases. Curtis and colleagues<sup>25</sup> found an eight-fold increase in the risk of brain cancer among bone-marrow transplant recipients, especially with high-dose total-body irradiation and no chronic graft-versus-host disease. After blood transfusion, people with AIDS rarely, if ever, have graft-versus-host disease<sup>26</sup>—a seemingly benign manifestation of their immune dysfunction, but one that may carry a risk of brain cancer. Infectious agents, particularly herpesviruses in testicular cancer and papovaviruses in brain cancer, have been postulated to contribute to these neoplasms, but the few studies have had mixed results.<sup>27–29</sup>

Anal cancer and cervical cancer are related to sexually transmitted human papillomavirus—especially genotypes 16 and 18—and probably to cigarette smoking also.<sup>30</sup> Despite their aetiological similarities, people with AIDS had paradoxical patterns of anal, cervical in-situ, and invasive cervical cancers (figure 4). As is consistent with our predominantly male homosexual AIDS population,

the early pre-AIDS risk of anal cancer was raised 15-fold,<sup>30</sup> and increased non-significantly after AIDS. The early pre-AIDS risk of invasive cervical cancer was increased five-fold but the risk of in-situ cancer was substantially reduced (0.7-fold), which suggests that HIV-1-infected women have less frequent cytological screening than do women in the general population. We speculate that, later in HIV-1 disease, the increasing risk of in-situ cancer and the stable or falling risk of invasive cervical cancer reflect an increasing rate of screening for—and treatment of—early neoplasia. Premalignant lesions of the cervix and anus have been associated with HIV-1-related immunodeficiency and especially with human-papillomavirus infection,<sup>2</sup> but prospective cohort analyses are needed to distinguish a true association of anogenital neoplasia due to AIDS from the effects of screening and treatments that occur during HIV-1 disease.

With the exception of KS, we found no association between AIDS and skin cancers, despite the well-established excess of these tumours in transplant recipients<sup>1,25</sup> and despite the fact that the people with AIDS in the AIDS-Cancer Match Registry were mostly white (60%) and from sunny locations (California, Florida, and Puerto Rico). People with AIDS had no increase in melanoma, which suggests that the increased risk for transplant recipients may result from azathioprine or ionising radiation therapy rather than from immunodeficiency. The risk of non-melanoma skin cancer for people with AIDS was increased five-fold. Perhaps this excess would be statistically significant if reporting of basal-cell and squamous-cell skin cancers to the registries was more complete.

The paradoxes and uncertainties with anal, cervical, and skin cancers reveal the limitations of registry analyses. In general, our study was large enough to accommodate the 5–10% of cancer cases that were not correctly linked by our matching algorithm,<sup>4</sup> but the study could not account for massive losses of unreported non-melanoma skin cancers. We had a fairly low proportion of women and children, and lacked data on covariates such as cigarette smoking or human-papillomavirus infection, which limited the interpretation of risks for some cancer types. Finally, because we investigated 38 different types of cancer, some positive associations with AIDS could have been due to chance. We believe that our criteria were sufficiently stringent to define an AIDS-associated cancer: the relative risk had to be raised in the post-AIDS period, and a trend with increasing relative risks had to be shown across the early pre-AIDS, later pre-AIDS, and post-AIDS periods. Replication of our findings is still needed, particularly for brain cancer and multiple myeloma, the results of which might have been biased by deficits of cases in the early pre-AIDS period.

We considered in depth several potential biases in the data and analyses in our study. First, we assumed that the HIV-1-infected population was resident in our cancer surveillance areas for at least 5 years before diagnosis of AIDS. However, migration of people with advanced HIV-1 infection into our survey areas would cause overestimation of the number of people thought to be under observation, thereby falsely lowering the prevalence of cases at earlier times before AIDS. To examine this potential bias, we calculated non-AIDS cancer frequencies in the earliest period: 25–60 months pre-AIDS. We found 166 linkages, whereas 172 would have

been expected (RR 0.97; table). Thus, the cancer-prevalence data in the early pre-AIDS period appear to be complete, and rising trends later in the course of HIV-1 disease are unlikely to be an artifact of migration into the cancer-surveillance area.

Second, prevalence ratios in the early pre-AIDS and later pre-AIDS periods are subject to survivorship bias. For a case to be prevalent in the early pre-AIDS period, a person must develop cancer 25–60 months before AIDS and survive until the time of AIDS diagnosis. If mortality rates after a cancer diagnosis in the early pre-AIDS period are the same in the general population and the HIV-1-infected population (before AIDS onset), then prevalence ratios would be unbiased and would reflect cancer-incidence ratios. However, mortality rates for some cancers might possibly be greater in the HIV-1-infected population, which would tend to lower the early pre-AIDS prevalence ratio and contribute slightly to a positive trend over time in risk ratios.

Third, estimates of RR in the post-AIDS period could be affected by biases in either direction. Latent cancers are detected incidentally during the medical assessment at the time of AIDS diagnosis, contributing to the high RRs for many cancers from months –6 to +3 (table). Many of these cancers, had they not been detected at the time of AIDS diagnosis, would have been incident in the post-AIDS period. This well-known screening effect<sup>31</sup> can reduce cancer incidence in the post-AIDS period; we previously recorded a reduced incidence rate of post-AIDS cancers, other than KS and NHL, compared with general-population rates.<sup>8</sup> Other factors that can lower post-AIDS incidence rates include unreported deaths and migration from the cancer surveillance areas.

To some extent, these reductions in post-AIDS rates are offset by continued intense medical surveillance in the post-AIDS period, which can induce a lead-time bias for disorders with incidence rates that rise steeply with age. We estimated the lead-time bias for a 2-year lead time by taking a weighted average of age-specific incidence rates at ages  $a+2$  and dividing this average by the weighted average age-specific incidence rates at age  $a$ , where the weights are in proportion to the person-years of exposure among people with AIDS in the age-groups 20–29, 30–39, 40–49, 50–59, and 60–69. For an age interval such as 20–29, the age-specific rate at  $a$  is estimated as the simple average of the SEER rates<sup>7</sup> over intervals 20–24 and 25–29, and the value at  $a+2$  is estimated as the previous average plus  $(2/5) \times ([\text{rate for } 25\text{--}29] - [\text{rate for } 20\text{--}24])$ . The proportions of person-years (weights) in these five age-groups were 0.224, 0.489, 0.212, 0.060, and 0.015, respectively. The lead-time biases in the RRs (table) for the post-AIDS period are –3% for Hodgkin's disease, 18% for other leukaemia, 25% for multiple myeloma, 10% for brain cancer, and 5% for seminoma or germinoma. These lead-time biases are small, especially compared with the countervailing biases from screening at AIDS diagnosis. The net effect of screening and post-AIDS surveillance bias is probably to reduce the estimated RRs in the post-AIDS period for most cancers.

Computer-based linking of registry data offers an efficient and cost-effective method to generate and test hypotheses on disease aetiology in vivo. Matching can also be used to improve the completeness of disease surveillance for each participating registry and for clarification of trends in diseases that may be biologically

inter-related, such as tuberculosis and AIDS. This activity, however, must be done under strict protocols to prevent disclosure of identifying information. Our matching was done with authorised registry personnel who have legal access to the reported data. The computer functioned as a true "black box" with no display or electronic copying of identifying information. During the match, all records were labelled with a code number only, and all identifying information was removed when the analysis file was created. Thus, the system revealed no personal information to the AIDS registry, the cancer registry, or the study investigators.<sup>4</sup>

Although the results for some types of cancer are ambiguous, there is no doubt that people with AIDS are at extraordinarily high risk of KS, almost certainly because of a transmissible agent, with current evidence pointing to human herpesvirus 8.<sup>19,32–34</sup> Although the temptation is to draw the general conclusion that AIDS-associated malignant disorders are predominantly those that result from activated or aberrant herpesvirus infection, nasopharyngeal carcinoma—which has been linked to aberrant Epstein-Barr-virus infection<sup>34,35</sup>—is not significantly increased among people with AIDS.<sup>36</sup> As with the strong genetic, dietary, and other environmental exposures that increase the risk of nasopharyngeal and hepatocellular carcinomas,<sup>35,37</sup> a viral infection probably does not cause an AIDS-associated malignant disorder by itself. Rather, heredity may be important in the determination of the immunological and non-immunological response to a viral infection, which in turn creates the intracellular and extracellular environment in which failures in mitosis checkpoints and DNA repair cause cancer.

We found that AIDS is associated with neoplasms already thought to be linked to common viruses. If these viruses are linked in this way, and if AIDS disrupts control over their oncogenic effects, cancer risks might reasonably be higher among people with AIDS. This study is not unlike those that follow transplant recipients, patients with congenital immunodeficiencies, or nude mice. The difference is one of scope: the AIDS epidemic has unfortunately provided a large human population that is susceptible to an intriguingly limited spectrum of cancers.

#### Contributors

James J Goedert designed and coordinated the current analysis and was primarily responsible for drafting the paper. Timothy R Coté conceived the AIDS Cancer Match Registry, developed the matching criteria, and established collaboration with the local AIDS and cancer registries. Phillip Virgo wrote the computer programs for matching the AIDS and cancer cases, carried out on-site matching, created the file of matched cases for the current analysis, and did the post-AIDS incidence analyses. Steven M Scoppa organised the census and surveillance, epidemiology, and end results files for the current analysis and carried out the prevalence analyses. Douglas W Kingma did the AIDS-lymphoma validation study and the Epstein-Barr virus testing. Mitchell H Gail supervised the statistical analysis, devised the test for trend, and carried out the screening and post-AIDS surveillance-bias analysis. Elaine S Jaffe did the AIDS-lymphoma validation analysis. Robert J Biggar supervised the current analysis and monitored the AIDS cancer match contractor. All authors contributed to the final text.

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The group includes representatives of the AIDS registry and the cancer registry in each location: George Lemp and Dee West (San Francisco); Jim Singleton and John Young (Sacramento); Peter Kerndt and Dennis Deapen (Los Angeles); Michelle Ginzberg and Hoda Anton-Culver (San Diego); Spencer Lieb and Richard Hopkins (Florida); Brian Williams and Jonathan Liff (Atlanta); Douglas Morgan and William Parkin (New Jersey); and Samuel Martinez Cardona and José Becerra (Puerto Rico).

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