

Association of Cancer With AIDS-Related Immunosuppression in Adults

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IMMUNOSUPPRESSION ASSOCIATED with human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) markedly increases the risk of Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL).¹ These malignancies and invasive cervical cancer are the only AIDS-defining cancers in HIV-infected individuals.² Other specific cancers also occur in excess, but the risk pattern depends on the geographic region and the HIV exposure group studied.^{3,4} In industrialized parts of the world, a high level of risk has been found for anal cancer⁵ and Hodgkin disease,⁶⁻⁸ and marginally significant increases were reported for seminoma, multiple myeloma, and brain cancer.^{7,8} We used data from the recently updated AIDS-Cancer Match Registry Study to investigate the cancer pattern in the years surrounding the time of AIDS diagnosis among 302834 adult persons with HIV/AIDS (PWAs) in the United States. Specifically, we aimed at identifying cancers that are likely to be influenced by immunosuppression, distinguishing them from those occurring in excess among PWAs due to lifestyle-related exposures linked to cancer risk independently of immunosuppression.

METHODS

We linked cancer data to 366034 PWAs from 11 areas, including the states of Connecticut, Florida, Illinois, Massa-

Context Large-scale studies are needed to determine if cancers other than Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer occur in excess in persons with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS).

Objectives To examine the general cancer pattern among adults with HIV/AIDS and to distinguish immunosuppression-associated cancers from other cancers that may occur in excess among persons with HIV/AIDS.

Design, Setting, and Subjects Analysis of linked population-based AIDS and cancer registry data from 11 geographically diverse areas in the United States, including 302834 adults aged 15 to 69 years with HIV/AIDS. The period of study varied by registry between 1978 and 1996.

Main Outcome Measure Relative risks (RRs) of cancers, calculated by dividing the number of observed cancer cases by the number expected based on contemporaneous population-based incidence rates. We defined cancers potentially influenced by immunosuppression by 3 criteria: (1) elevated overall RR in the period from 60 months before to 27 months after AIDS; (2) elevated RR in the 4- to 27-month post-AIDS period; and (3) increasing trend in RR from before to after AIDS onset.

Results Expected excesses were observed for the AIDS-defining cancers, but non-AIDS-defining cancers also occurred in statistically significant excess ($n=4422$; overall RR, 2.7; 95% confidence interval [CI], 2.7-2.8). Of individual cancers, only Hodgkin disease ($n=612$; RR, 11.5; 95% CI, 10.6-12.5), particularly of the mixed cellularity ($n=217$; RR, 18.3; 95% CI, 15.9-20.9) and lymphocytic depletion ($n=36$; RR, 35.3; 95% CI, 24.7-48.8) subtypes; lung cancer ($n=808$; RR, 4.5; 95% CI, 4.2-4.8); penile cancer ($n=14$; RR, 3.9; 95% CI, 2.1-6.5); soft tissue malignancies ($n=78$; RR, 3.3; 95% CI, 2.6-4.1); lip cancer ($n=20$; RR, 3.1; 95% CI, 1.9-4.8); and testicular seminoma ($n=115$; RR, 2.0; 95% CI, 1.7-2.4) met all 3 criteria for potential association with immunosuppression.

Conclusion Although occurring in overall excess, most non-AIDS-defining cancers do not appear to be influenced by the advancing immunosuppression associated with HIV disease progression. Some cancers that met our criteria for potential association with immunosuppression may have occurred in excess in persons with HIV/AIDS because of heavy smoking (lung cancer), frequent exposure to human papillomavirus (penile cancer), or inaccurately recorded cases of Kaposi sarcoma (soft tissue malignancies) in these persons. However, Hodgkin disease, notably of the mixed cellularity and lymphocytic depletion subtypes, and possibly lip cancer and testicular seminoma may be genuinely influenced by immunosuppression.

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chusetts, New Jersey, and New York, and the metropolitan areas of Atlanta, Los Angeles, San Diego, San Francisco, and Seattle. Commercially available software (AutoMatch versions 3.0 and 4.1; MatchWare Technologies Inc, Burtonsville, Md) was used to implement a probabilistic matching algorithm that

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evaluated the likelihood of subject linkage on the basis of identical or near-identical information in AIDS and cancer registries. Before data linkage, we obtained institutional review board approval at all participating AIDS and cancer registries to ensure patient confidentiality. Details of the linkage procedure have been described elsewhere.⁹

This study describes the cancer profile of 302834 adults (age 15-69 years) diagnosed with AIDS between 1978 and 1996. We excluded 56669 persons whose AIDS diagnoses occurred outside the period when corresponding cancer registries were considered complete, 4954 children aged 0 to 14 years at AIDS diagnosis (dealt with in detail elsewhere¹⁰), and 1577 persons aged 70 years or older at AIDS diagnosis. The period covered varied by registry, but all regions included the 12-year period from January 1983 through December 1994, except San Diego, where cancer registration started in January 1988. For 2.3% of the study subjects, we backdated the onset of AIDS to the date of an AIDS-defining cancer (KS, n=5155; NHL, n=1731; invasive cervical cancer, n=182) recorded in the cancer registry up to 5 years before the date of onset recorded in the AIDS registry. In examining the non-AIDS-defining cancers, we studied only invasive cancers and used the *International Classification of Diseases for Oncology*, second edition¹¹ to define cancer categories. Analyses were made for KS, NHL, and for specific sites (excluding KS and NHL). We studied all cancer types, except non-melanoma skin cancers. The latter were disregarded, because non-melanoma skin cancers are incompletely recorded in cancer registries and may include inadequately recorded cases of KS, the single most common cancer among PWAs.

Measures of Relative Risk

Using methods similar to those of a previous study,⁷ which assessed cancer risks in persons diagnosed with AIDS between 1978 and 1990, we studied the relative risk (RR) of cancer from 60 months before to 27 months after AIDS onset in the following intervals: from 60

to 25 months before AIDS (*distant pre-AIDS period*, during which most of the PWAs were likely to be HIV-infected but unlikely to have developed severe immunosuppression), from 24 to 7 months before AIDS (*recent pre-AIDS period*, during which most of the PWAs approached the time of opportunistic infections and cancers that define AIDS), from 6 months before to 3 months after AIDS (*AIDS period*), and from 4 to 27 months after AIDS (*early post-AIDS period*, which was truncated at 2 years after the AIDS period to avoid an overestimation of the number of PWAs under surveillance). To extract the maximum information available for rare cancers (ie, those with <25 cases), we also studied cancers occurring from 28 to 60 months after AIDS (*late post-AIDS period*, which was used only in the evaluation of pre- to post-AIDS trends for rare cancers). For each interval, the RR was the ratio of observed to expected cancers derived from contemporaneous population-based incidence rates. By definition, all PWAs who had cancer in the 5 years prior to AIDS survived long enough after their cancer diagnosis to develop AIDS. Failure to take this survival factor into account has a major impact on the RR estimates.⁸ Consequently, estimates of the expected cancers, to which observed cases were compared, had to take into account that some individuals developed cancer and died or were lost to follow-up before they developed AIDS. To do so, we calculated survival-conditioned cancer incidence rates covering each month back to 5 years before AIDS, as described elsewhere.⁹ Because reliable cancer survival data are not available for HIV-infected persons, we used cancer survival data from the Surveillance, Epidemiology, and End Results (SEER) program for the period 1981-1993 to adjust the pre-AIDS incidence rates. The resulting survival-conditioned cancer incidence rates were calculated for the 11 regions combined, in strata of sex, race (white, black, other/unknown), and age (5-year age groups). Stratum-specific monthly survival-conditioned incidence rates were multiplied by the ap-

propriate person-months of observation among the PWAs and the products were summed to yield the expected number of pre-AIDS cancers. For the post-AIDS periods, we constructed 1 combined set of sex-, race-, age-, and period-specific incidence rates for the 11 regions under study. Expected numbers of cancers were calculated as the sum of stratum-specific products of background cancer incidence and person-months at risk among the PWAs.¹²

To provide an overall RR estimate, we used the sum of observed cancers over the sum of expected cancers for the 7.25-year period from 60 months before to 27 months after AIDS. We did not include cancers from the late post-AIDS period in this overall RR measure because the number of PWAs under observation in this interval may have been overestimated (and RRs underestimated) due to unrecorded late deaths and migration out of the catchment areas. For the AIDS-defining cancers, we only provide an estimate of the RR in the early post-AIDS period since, by definition, none of these cancers occurred before AIDS. We calculated 95% confidence intervals (CIs) assuming a Poisson distribution of the observed cancers.¹² When zero cancers occurred, 1-sided exact 95% CIs are provided with the upper confidence limit calculated as $[-\ln(0.05)/\text{expected number of cancers}]$. The RRs were calculated by sex, ethnic group (white, black, Hispanic, other/unknown), and HIV exposure group (homosexual contact [including homosexual intravenous drug users, men only]; heterosexual contact; non-homosexual intravenous drug users; patients infected during treatment for hemophilia or other bleeding disorders, or via transfusion or transplantation; and other/unknown HIV exposure), according to AIDS registry information. Sex-, ethnic group-, and age-specific background rates were used to calculate expecteds in all analyses. Since background cancer rates were not available for Hispanics, expected cancers in this group were based on cancer rates for whites.

Malignancies may occur in excess among PWAs for reasons unrelated to

Table 1. Demographic Characteristics and Route of HIV Transmission Among 302 834 Adults (Age 15-69 Years) With AIDS, AIDS-Cancer Match Registry Study, United States, 1978-1996*

Characteristic	Men, No. (%)	Women, No. (%)
Age at AIDS diagnosis, y		
15-29	39 056 (15.4)	11 243 (23.0)
30-39	116 987 (46.1)	23 532 (48.1)
40-49	70 252 (27.7)	10 334 (21.1)
50-59	21 403 (8.4)	2 776 (5.7)
60-69	6 187 (2.4)	1 064 (2.2)
15-69	253 885 (100)	48 949 (100)
Median (range)	37 (15-69)	35 (15-69)
Year of diagnosis, median (range)	1991 (1978-1996)	1992 (1979-1996)
Ethnic group		
White	121 464 (47.8)	10 497 (21.4)
Black	80 526 (31.7)	28 020 (57.2)
Hispanic	49 134 (19.4)	10 093 (20.6)
Other/unknown	2 761 (1.1)	339 (0.7)
Route of HIV acquisition		
Homosexual contact	143 619 (56.6)	...
Homosexual contact + intravenous drug use	15 674 (6.2)	...
Heterosexual contact		
With unspecified partner of opposite sex	7 782 (3.1)	7 312 (14.9)
With bisexual male partner	...	1 249 (2.6)
With nonbisexual male partner	...	8 709 (17.8)
Intravenous drug use†	67 096 (26.4)	24 258 (49.6)
Transfusion or transplantation	1 656 (0.7)	1 361 (2.8)
Hemophilia or other bleeding disorders	1 347 (0.5)	105 (0.2)
Unknown‡	16 711 (6.6)	5 955 (12.2)

*HIV indicates human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; and ellipses, not applicable.

†Excludes male homosexual intravenous drug users.

‡Includes 1 male and 2 females who were HIV-infected vertically.

immunosuppression such as smoking and exposure to sexually transmitted human papillomavirus. To identify cancers that are likely to be influenced by the waning immune competence during the course of HIV infection and AIDS, we expanded previously defined criteria⁷ to also include the demand for a statistically significantly elevated overall RR. Specifically, a cancer was considered potentially influenced by immunosuppression when all of 3 criteria were met: (1) the overall RR for the period from 60 months before to 27 months after AIDS was significantly elevated; (2) the RR in the early post-AIDS period was significantly elevated; and (3) there was a statistically significant increasing trend in the RRs from before to after AIDS onset. To evaluate the trend, we modeled the RR in a Poisson regression model as: $\ln(O_i/E_i) = \alpha + \beta t_i$, where O_i and E_i were the observed and expected numbers of

cancers, respectively, in the individual periods included in the trend test, and α was the sum of observed divided by the sum of expected cancers for periods contributing information to the trend test (with t_i , the midpoint of the time interval, measured from AIDS onset). In this model, a 2-sided score test¹³ of $\beta=0$ evaluated whether RR changed over time. We attributed the observation of rather extreme RRs in the AIDS period for cancers at most sites to the generally increased diagnostic activity around the time of AIDS diagnosis (ascertainment bias). To avoid the influence of such ascertainment bias, we disregarded cancers occurring in the AIDS period in the trend test. Consequently, we used information from the distant and recent pre-AIDS periods and the early post-AIDS period in trend tests, using midpoints for these intervals ($t = -42.5, -15.5,$ and 15.5 months, respectively) as values of t_i . However,

for cancers with fewer than 25 observed cases, we also included data from the late post-AIDS period ($t = 44$ months) in the trend test, to use the maximum information available. Since underascertainment of deaths and migration out of the catchment areas renders the person-time at risk in the late post-AIDS period too high, and thus the corresponding RR too low, the trend test for these less common cancers is likely to be conservative.

We performed 2 sensitivity analyses to assess the robustness of our findings. In one, we based the trend test only on cancers occurring in the 2 pre-AIDS periods and the AIDS period (t values of $-42.5, -15.5,$ and -1.5 months, respectively). This test is likely to be biased toward finding too many positive trends because of high RRs in the AIDS period due to ascertainment bias, as described above. In the second, we split the AIDS-relative time axis into 3 new pre-AIDS periods (60 to 41 months, 40 to 21 months, and 20 to 7 months before AIDS), the AIDS period (6 months before to 3 months after AIDS), and 2 new post-AIDS periods (4 to 24 months and 25 to 60 months after AIDS), using midpoints for the pre-AIDS periods ($t = -50.5, -30.5,$ and -13.5 months) and the early post-AIDS period ($t = 14$ months). When numbers of cancers were small (<25), we also used the late post-AIDS period ($t = 42.5$ months) in trend tests.

RESULTS

Demographic characteristics and route of HIV acquisition for the 302 834 adult PWAs are shown in TABLE 1. Nearly half were between 30 and 39 years old at AIDS onset and most were younger than 50 years. Whites were the largest group among men (47.8%), whereas blacks predominated among women (57.2%). Homosexual men (including homosexual intravenous drug users) constituted 62.8% of the men, and an additional 26.4% were non-homosexual intravenous drug users. Only 3.1% of the men were HIV-infected through heterosexual contact. Among women, 49.6% were infected through

intravenous drug use, and 35.3% were infected heterosexually (Table 1).

AIDS-Defining Cancers

Among men, KS was an AIDS-defining cancer or occurred within 27 months after another AIDS-defining event in 20848 persons (9.9%), while NHL occurred in 8622 persons (3.4%). Among women, corresponding numbers were 307 KS cases (0.8%), 728 NHL cases (1.5%), and 348 invasive cervical cancer cases (0.7%). Among men, the post-AIDS RR for KS (n=5823; RR, 175.8) was highest among homosexual PWAs (n=5410; RR, 267.2) while, among women, the post-AIDS RR for KS (n=113; RR, 405.2) was highest among those who were HIV-infected by a bisexual man (n=11; RR, 2044.2). The post-AIDS RR for NHL was 72.8, with RRs of 71.7 among men (n=3073) and 88.4 among women (n=271). The post-AIDS RR for cervical cancer was 5.2 (n=46) (TABLE 2).

Non-AIDS-Defining Cancers

Overall, 4422 invasive cancers other than AIDS-defining cancers and non-melanoma skin cancers occurred vs 1611.3 expected (RR, 2.7; 95% CI, 2.7-2.8). The overall excess of non-AIDS-defining cancers was seen in both men (n=3757; RR, 2.8; 95% CI, 2.7-2.9) and women (n=665; RR, 2.4; 95% CI, 2.2-2.6). Significant overall excesses were seen for cancers at several sites (Table 2). Of the more than 60 individual cancer types studied, all 3 criteria for potential association with immunosuppression were met only for 6 cancers: Hodgkin disease, lip cancer, lung cancer, soft tissue malignancies, penile cancer, and testicular seminoma (Table 2, FIGURE). Other/unspecified lymphatic/hematopoietic cancers, unspecified types of cancer of brain and central nervous system, and cancers at unknown or ill-defined primary sites also met all 3 criteria. However, these latter groups of unspecified cancers likely comprise considerable proportions of the much more common AIDS-defining cancers, notably inaccurately classified cases of NHL, including brain lymphoma. It

should be noted that for data assessed by trend test (Figure), the generally higher frequency of cancers occurring in the AIDS period is likely, in part, to be an artifact of ascertainment bias. Because it is impossible to know the extent of possible bias, cancer data from the AIDS period were not included in the trend test.

Cancers Potentially Influenced by Immunosuppression

Hodgkin Disease. The overall RR for Hodgkin disease (n=612) was 11.5-fold increased, being higher in men (n=558; RR, 12.0) than in women (n=54; RR, 8.3) (TABLE 3). However, for each sex, differences were small among the major HIV exposure categories (men: homosexual contact [n=386; RR, 12.5]; heterosexual contact [n=14; RR, 11.0]; intravenous drug use [n=121; RR, 10.7]; women: heterosexual contact [n=17; RR, 7.0]; intravenous drug use [n=25; RR, 7.7]). For men and women combined, the RR increased from 2.6 in the distant pre-AIDS period to 9.8 in the recent pre-AIDS period and 6.7 in the early post-AIDS period (*P* for trend, <.001) (Figure). Significant trends were seen in separate analyses for men (*P*<.001) and women (*P*=.04), and for subgroups of homosexual men (*P*<.001) and intravenous drug-using men (*P*=.004).

The expected distribution of histologic subtypes of Hodgkin disease was nodular sclerosis (64%), mixed cellularity (26%), lymphocytic predominance (8%), and lymphocytic depletion (2%). For PWAs with histologically specified Hodgkin disease (n=403), the excess was much greater for mixed cellularity (54%; overall RR, 18.3) and lymphocytic depletion (9%; overall RR, 35.3) than for nodular sclerosis (34%; overall RR, 4.7) or lymphocytic predominance (3%; overall RR, 3.0) (Table 2). In the distant pre-AIDS period, RRs for the mixed cellularity (n=25; RR, 5.2) and lymphocytic depletion (n=2; RR, 4.8) subtypes were already increased, but not for nodular sclerosis (n=12; RR, 0.9) or lymphocytic predominance (0 observed vs 1.6 expected) subtypes. Even in the late post-AIDS period, the RR remained signifi-

cantly high for the mixed cellularity subtype (n=7; RR, 7.7; 95% CI, 3.1-15.9).

Lung Cancer. Lung cancer (n=808) was the most frequently diagnosed non-AIDS-defining cancer. The RRs increased from 1.2 in the distant pre-AIDS period to 2.7 in the recent pre-AIDS period and 2.8 in the early post-AIDS period (*P* for trend<.001) (Figure). The crude lung cancer incidence in the early post-AIDS period was slightly higher in male than female PWAs (80.1 vs 68.0 per 100000), but the overall RR was higher in women (RR, 7.1) than men (RR, 4.3) (Table 3). Although many women developed lung cancer (n=110), the pre- to post-AIDS trend was significant only in men and in subgroups of whites (*P*=.002) and homosexuals (*P*<.001). All 3 statistical criteria for potential association with immunosuppression were met for squamous cell carcinoma, adenocarcinoma, and other and unspecified types of lung cancer (Table 2).

Penile Cancer. Anogenital cancers of the cervix, anus, vulva/vagina, and penis occurred in significant overall excess, but the trend test was significant only for penile cancer (n=14) (Table 2, Figure). Blacks, Hispanics, and intravenous drug users were at particularly elevated risk (Table 3).

Soft Tissue Malignancies. Seventy-eight malignant tumors originated in soft tissues (overall RR, 3.3) (Table 2). Twenty-five (32%) were histologically unspecified, 14 (18%) were soft tissue sarcomas, and 12 (15%) were leiomyosarcomas. Including 6 leiomyosarcomas at sites other than soft tissues, the overall RR for leiomyosarcoma was 2.3 (Table 2). The excess risk for leiomyosarcoma was statistically significant only among the 15- to 29-year-old PWAs (n=7; overall RR, 17.3; 95% CI, 6.9-35.7). Angiosarcomas occurred in approximately 13-fold excess, but the trend test was not significant (Table 2).

Lip Cancer. The overall RR for lip cancer was 3.1 (Table 2). All 20 cases of lip cancer occurred in males, but only 0.14 cases were expected in women. For men and women combined, RRs increased steadily from 1.6 in the

Table 2. Relative Risk of Cancer Among 302 834 Adults (Age 15-69 Years) With AIDS From 60 Months Before to 27 Months After AIDS Onset, AIDS-Cancer Match Registry Study, United States, 1978-1996*

Cancer†	Pre- to Post-AIDS Period‡ (-60 to +27 mo)		Early Post-AIDS Period§ (+4 to +27 mo)		P Value for Pre- to Post-AIDS Trend
	No. of PWAs With Cancer	RR (95% CI)	No. of PWAs With Cancer	RR (95% CI)	
AIDS-defining cancers					
Kaposi sarcoma¶	21 155	NA	5936	177.7 (173.2-182.3)	NA
Non-Hodgkin lymphoma	9350	NA	3344	72.8 (70.4-75.3)	NA
Cervical carcinoma	348	NA	46	5.2 (3.8-6.9)	NA
Non-AIDS-defining cancers	4422	2.7 (2.7-2.8)	1127	2.1 (2.0-2.3)	<.001
Lymphatic/hematopoietic system, except non-Hodgkin lymphoma	1008	8.0 (7.5-8.5)	195	5.3 (4.6-6.1)	<.001
Leukemia, overall	175	3.6 (3.1-4.1)	35	2.1 (1.5-2.9)	.57
ALL	37	7.4 (5.2-10.3)	2	1.1 (0.1-3.9)	.99
CLL	12	0.9 (0.5-1.7)	2	0.6 (0.1-2.3)	.30
ATLL	10	44.5 (21.4-81.9)	2	14.7 (1.8-52.9)	.93
AML	35	4.2 (2.9-5.9)	10	2.5 (1.2-4.5)	.15
CML	19	1.6 (1.0-2.5)	2	0.6 (0.1-2.1)	.06
Other/unspecified leukemias	62	6.2 (4.7-7.9)	17	4.3 (2.5-6.8)	.23
Hodgkin disease	612	11.5 (10.6-12.5)	81	6.7 (5.3-8.3)	<.001
Mixed cellularity	217	18.3 (15.9-20.9)	24	9.1 (5.8-13.5)	.02
Lymphocytic depletion	36	35.3 (24.7-48.8)	3	10.7 (2.2-31.2)	.39
Lymphocytic predominance	11	3.0 (1.5-5.4)	1	1.3 (0.0-7.2)	.56
Nodular sclerosis	139	4.7 (3.9-5.5)	18	2.8 (1.7-4.5)	.002
Unspecified types	209	31.8 (27.6-36.4)	35	17.2 (12.0-23.9)	.02
Multiple myeloma	49	2.6 (1.9-3.4)	10	1.7 (0.8-3.0)	.70
Other/unspecified lymphatic/ hematopoietic cancers	172	32.8 (28.1-38.1)	69	31.1 (24.2-39.3)	<.001
Lip, oral cavity, and pharynx	260	2.7 (2.4-3.1)	70	2.3 (1.8-2.9)	.054
Lip	20	3.1 (1.9-4.8)	7	5.1 (2.0-10.4)	.04
Tongue	54	2.8 (2.1-3.6)	12	1.7 (0.9-3.0)	.42
Other mouth	74	3.1 (2.4-3.9)	23	3.2 (2.0-4.7)	.35
Salivary glands	21	2.5 (1.5-3.8)	4	1.8 (0.5-4.5)	.84
Tonsil	29	2.4 (1.6-3.5)	8	1.8 (0.8-3.6)	.37
Oropharynx	17	6.0 (3.5-9.7)	3	2.3 (0.5-6.7)	.71
Nasopharynx	27	2.6 (1.7-3.7)	6	2.8 (1.0-6.1)	.26
Digestive organs	637	2.3 (2.1-2.5)	166	1.6 (1.3-1.8)	.08
Esophagus	33	1.6 (1.1-2.3)	13	1.2 (0.7-2.1)	.10
Stomach	60	2.0 (1.5-2.5)	22	1.6 (1.0-2.4)	.08
Small intestine	10	1.3 (0.6-2.4)	1	0.4 (0.0-2.1)	.72
Colon/rectum	158	0.9 (0.8-1.04)	34	0.6 (0.4-0.9)	.80
Anus, not specified as SCC	16	11.9 (6.8-19.2)	7	14.3 (5.7-29.5)	.57
Anus, SCC	221	33.8 (29.5-38.6)	50	22.8 (16.9-30.0)	.95
Liver/intrahepatic bile ducts	87	7.7 (6.1-9.4)	23	3.1 (2.0-4.6)	.25
Pancreas	45	2.4 (1.7-3.2)	15	1.3 (0.7-2.2)	.82
Respiratory and intrathoracic organs	960	4.1 (3.9-4.4)	271	2.6 (2.3-2.9)	<.001
Larynx	118	2.8 (2.3-3.3)	21	1.7 (1.1-2.6)	.97
Lung#	808	4.5 (4.2-4.8)	241	2.8 (2.4-3.1)	<.001
Small cell carcinoma	68	3.2 (2.5-4.1)	22	2.0 (1.2-2.9)	.66
SCC	191	4.3 (3.7-4.9)	59	2.9 (2.2-3.7)	.02
Adenocarcinoma	228	4.4 (3.9-5.1)	60	2.4 (1.9-3.1)	.04
Bronchioloalveolar carcinoma	15	3.2 (1.8-5.3)	3	1.8 (0.4-5.1)	.43
Other/unspecified lung cancer	313	5.4 (4.8-6.0)	98	3.4 (2.7-4.1)	.02
Heart, mediastinum, pleura	20	4.6 (2.8-7.1)	5	2.5 (0.8-5.9)	.51

Table 2. Relative Risk of Cancer Among 302 834 Adults (Age 15-69 Years) with AIDS From 60 Months Before to 27 Months After AIDS Onset, AIDS-Cancer Match Registry Study, United States, 1978-1996* (cont)

Cancer	Pre- to Post-AIDS Period† (-60 to +27 mo)		Early Post-AIDS Period§ (+4 to +27 mo)		P Value for Pre- to Post-AIDS Trend
	No. of PWAs With Cancer	RR (95% CI)	No. of PWAs With Cancer	RR (95% CI)	
Malignant melanoma	145	1.3 (1.1-1.6)	27	1.0 (0.7-1.5)	.83
Soft tissues	78	3.3 (2.6-4.1)	25	3.6 (2.3-5.3)	<.001
Angiosarcoma	23	13.4 (8.5-20.1)	7	12.9 (5.2-26.6)	.14
Leiomyosarcoma	18	2.3 (1.4-3.6)	6	2.3 (0.9-5.1)	.12
Breast	143	1.1 (0.9-1.2)	17	0.5 (0.3-0.8)	.02
Female genital organs**	57	1.7 (1.3-2.2)	14	1.5 (0.8-2.5)	.62
Vulva/vagina	18	6.8 (4.1-10.8)	8	10.5 (4.5-20.8)	.64
Corpus uteri	12	0.9 (0.5-1.5)	3	0.8 (0.2-2.4)	.69
Ovary	23	1.5 (1.0-2.3)	2	0.5 (0.1-1.6)	.96
Male genital organs	328	1.1 (1.0-1.2)	70	0.8 (0.6-1.0)	.61
Penis	14	3.9 (2.1-6.5)	5	5.1 (1.7-11.9)	.046
Prostate	145	0.7 (0.6-0.9)	35	0.5 (0.4-0.7)	.10
Testicular seminoma	115	2.0 (1.7-2.4)	22	1.8 (1.1-2.6)	.003
Testicular non-seminoma	52	1.4 (1.0-1.8)	8	1.0 (0.4-2.0)	.51
Urinary system	128	1.0 (0.8-1.1)	33	0.9 (0.6-1.2)	.16
Kidney	79	1.5 (1.2-1.8)	21	1.2 (0.7-1.8)	.45
Bladder	41	0.6 (0.4-0.8)	7	0.4 (0.2-0.8)	.69
Eye	10	2.0 (1.0-3.7)	4	3.1 (0.8-8.0)	.87
Brain and CNS	156	3.5 (3.0-4.1)	55	3.6 (2.7-4.7)	<.001
Specified types	72	1.7 (1.4-2.2)	14	1.0 (0.5-1.6)	.31
Astrocytoma	33	1.7 (1.2-2.4)	6	1.1 (0.4-2.4)	.25
Glioblastoma multiforme	15	1.6 (0.9-2.7)	2	0.4 (0.1-1.4)	.85
Unspecified types	84	42.1 (33.6-52.1)	41	46.3 (33.2-62.7)	<.001
Thyroid	34	0.8 (0.5-1.1)	6	0.6 (0.2-1.3)	.96
Cancer at unknown or ill-defined primary sites	454	14.8 (13.4-16.2)	170	10.3 (8.8-12.0)	<.001

*AIDS indicates acquired immunodeficiency syndrome; PWA, persons with human immunodeficiency virus infection or AIDS; RR, relative risk; CI, confidence interval; NA, not analyzed; ALL, acute lymphoid leukemia; CLL, chronic lymphoid leukemia; ATLL, adult T-cell leukemia/lymphoma; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; SCC, squamous cell carcinoma; and CNS, central nervous system.

†Specified types of cancer that meet all 3 criteria for potential association with immunosuppression are marked in bold type. These criteria include the following: (1) a statistically significantly elevated overall RR for the period from 60 months before to 27 months after AIDS; (2) a statistically significantly elevated RR in the early post-AIDS period; and (3) a statistically significant increasing pre- to post-AIDS trend in the RR.

‡Numbers for the AIDS-defining cancers pertain to the AIDS period and the early post-AIDS period. All cancers other than non-melanoma skin cancers with 10 or more cases are listed in the table. Not listed are 77 cancers at the following sites: Pyriform sinus (n = 5), hypopharynx (n = 5), lip/oral cavity/pharynx, not otherwise specified (NOS) (n = 8), gallbladder (n = 2), other biliary tract (n = 4), gastrointestinal organs, NOS (n = 1), nasal cavities and middle ear (n = 5), accessory sinuses (n = 6), trachea (n = 1), thymus (n = 2), bones/joints/cartilage (n = 9), retroperitoneum/peritoneum (n = 3), uterus, NOS (n = 3), placenta (n = 1), male genital organs, NOS (n = 2), renal pelvis (n = 5), ureter (n = 2), urinary organs, NOS (n = 1), meninges (n = 2), adrenal glands (n = 8), and other endocrine organs (n = 2).

§Persons were considered at risk for Kaposi sarcoma, non-Hodgkin lymphoma, or cervical cancer in the early post-AIDS period only if they had not already been diagnosed with Kaposi sarcoma, non-Hodgkin lymphoma, or cervical cancer, respectively, in connection with the AIDS diagnosis.

||All P values are 2-sided. All P values <.05 indicate statistically significant increasing trends in the RR from the pre-AIDS to the post-AIDS period, except for breast cancer, where RRs decreased significantly from the pre-AIDS to the post-AIDS period.

¶Numbers and post-AIDS RR for Kaposi sarcoma are based on 250 150 PWAs (211 246 men and 38 904 women) in all geographical areas studied, except Florida.

#Seven patients had 2 types of lung cancer.

**Involving female genital organs other than cervical cancer.

distant pre-AIDS period to 5.8 in the late post-AIDS period (P for trend = .04).

Testicular Seminoma. Of 167 testicular cancers, 115 (69%) were seminomas. The RR for testicular seminoma was 0.7 in the distant pre-AIDS period, 2.0 in the recent pre-AIDS period, and 1.8 in the early post-AIDS period (P for trend = .003). The majority of seminomas (78%) occurred in homosexual men (RR, 2.2) (Table 3). A

high risk was seen in hemophilia patients (RR, 14.5; 95% CI, 3.9-37.1), but numbers were small (n = 4).

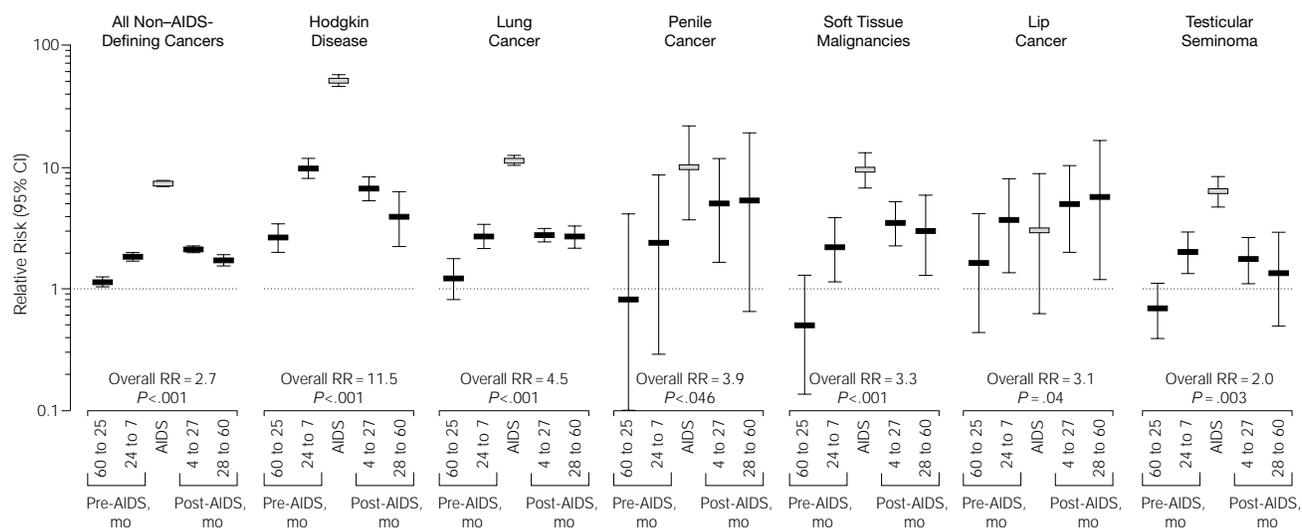
Other Cancers

Other cancers occurred in excess overall or in the early post-AIDS period (Table 2), including leukemia, multiple myeloma, and cancers of the oral cavity, salivary glands, pharynx, esophagus, stomach, anus, liver and intrahepatic bile

ducts, pancreas, larynx, heart, mediastinum and pleura, vulva/vagina, kidney, and specified types of brain and central nervous system cancers, as well as melanoma, testicular non-seminoma, and conjunctival carcinoma (n = 7; overall RR, 14.0; 95% CI, 5.6-28.8). None of these met the criterion of increasing trend in RR in relation to AIDS onset.

The pattern for breast cancer was unusual. Overall, the number of breast

Figure. Relative Risks in Relation to Time of AIDS Onset for Non-AIDS-Defining Cancers That Met Predefined Statistical Criteria for Potential Association With AIDS-Related Immunosuppression



The statistically significant overall relative risk (RR) with 95% confidence interval (CI) (period from 60 months before AIDS to 27 months after AIDS onset) and the 2-sided P value for pre- to post-AIDS trend in RR are provided for each cancer category. Trend tests are based on cancer risks in the distant pre-AIDS period (-60 to -25 months), the recent pre-AIDS period (-24 to -7 months), the early post-AIDS period (4 to 27 months) and, for penile cancer and lip cancer, the late post-AIDS period (28 to 60 months) and exclude the AIDS period (6 months before through 3 months after AIDS diagnosis; gray bars). AIDS indicates acquired immunodeficiency syndrome; HIV, human immunodeficiency virus. Error bars indicate 95% confidence intervals.

Table 3. Selected Non-AIDS-Defining Cancers Among 302 834 Adults (Age 15-69 Years) With AIDS, Post-AIDS Incidence and Overall Relative Risks (RRs) by Sex, Ethnic Group, and HIV Exposure, AIDS-Cancer Match Registry Study, United States, 1978-1996*

	Non-AIDS-Defining Cancers, Overall	Hodgkin Disease	Lung Cancer	Penile Cancer	Soft Tissue Malignancies	Lip Cancer	Testicular Seminoma
No. of Observed Cancers (Incidence per 100 000 Person-years) in Period 4-27 mo After AIDS Onset							
	1127 (365.5)	81 (26.3)	241 (78.2)	5 (1.6)	25 (8.1)	7 (2.3)	22 (7.1)
No. of Observed Cancers (Overall RR [95% CI]) for Period From 60 mo Before to 27 mo After AIDS Onset†							
Sex							
Men	3757 (2.8 [2.7-2.9])	558 (12.0 [11.0-13.0])	698 (4.3 [4.0-4.6])	14 (3.9 [2.1-6.5])	72 (3.4 [2.7-4.3])	20 (3.2 [1.9-4.9])	115 (2.0 [1.7-2.4])
Women	665 (2.4 [2.2-2.6])	54 (8.3 [6.2-10.8])	110 (7.1 [5.9-8.6])	...	6 (1.9 [0.7-4.2])	0 (0 [0-21.4])	...
Men and women	4422 (2.7 [2.7-2.8])	612 (11.5 [10.6-12.5])	808 (4.5 [4.2-4.8])	14 (3.9 [2.1-6.5])	78 (3.3 [2.6-4.1])	20 (3.1 [1.9-4.8])	115 (2.0 [1.7-2.4])
Ethnic group							
White	2133 (2.9 [2.8-3.0])	316 (11.7 [10.4-13.0])	340 (4.5 [4.1-5.0])	3 (1.9 [0.4-5.5])	31 (2.9 [2.0-4.2])	19 (4.3 [2.6-6.6])	93 (2.5 [2.0-3.0])
Black	1533 (2.8 [2.7-2.9])	169 (12.5 [10.7-14.5])	379 (4.9 [4.4-5.4])	8 (5.5 [2.4-10.9])	22 (2.5 [1.6-3.8])	1 (4.3 [0.1-23.9])	7 (1.9 [0.8-4.0])
Hispanic‡	711 (2.4 [2.2-2.6])	124 (10.2 [8.5-12.2])	81 (3.2 [2.5-4.0])	3 (5.6 [1.1-16.2])	22 (5.0 [3.2-7.6])	0 (0 [0-1.9])	15 (1.0 [0.6-1.6])
Other/unknown	45 (2.7 [2.0-3.6])	3 (9.5 [2.0-27.8])	8 (6.9 [3.0-13.6])	0 (0 [0-69.9])	3 (12.3 [2.5-36.0])	0 (0 [0-22.4])	0 (0 [0-7.2])
HIV exposure							
Homosexual§	2308 (2.9 [2.8-3.0])	386 (12.5 [11.3-13.8])	336 (3.7 [3.3-4.1])	6 (2.9 [1.1-6.3])	60 (4.7 [3.6-6.0])	16 (3.5 [2.0-5.7])	90 (2.2 [1.8-2.7])
Heterosexual	366 (2.2 [2.0-2.4])	31 (8.4 [5.7-11.9])	65 (4.2 [3.3-5.4])	0 (0 [0-18.2])	3 (1.6 [0.3-4.7])	0 (0 [0-15.1])	1 (0.9 [0.0-5.2])
Intravenous drug use	1213 (2.9 [2.7-3.0])	146 (10.0 [8.5-11.8])	310 (6.8 [6.1-7.6])	7 (7.2 [2.9-14.8])	5 (0.7 [0.2-1.7])	3 (2.7 [0.6-8.0])	17 (1.4 [0.8-2.2])
Hemophilia/transfusion	144 (2.8 [2.3-3.3])	7 (9.9 [4.0-20.4])	12 (1.9 [1.0-3.4])	0 (0 [0-39.0])	1 (2.4 [0.1-13.3])	1 (5.2 [0.1-28.8])	5 (9.7 [3.1-22.5])
Unknown	391 (2.4 [2.1-2.6])	42 (12.6 [9.1-17.1])	85 (4.3 [3.4-5.3])	1 (3.0 [0.1-16.9])	9 (4.7 [2.2-8.9])	0 (0 [0-7.4])	2 (0.8 [0.1-3.0])

*AIDS indicates acquired immunodeficiency syndrome; HIV, human immunodeficiency syndrome; RR, relative risk; CI, confidence interval; and ellipses, not applicable. †For all cancers, the RR is the ratio of observed to expected cancers for the period 60 months before to 27 months after AIDS. When zero cancers were observed, exact 1-sided 95% CIs are provided.

‡Expected numbers of cancers among Hispanics are based on cancer incidence rates among whites.

§Men only; includes homosexual men who use intravenous drugs.

||Includes persons who were HIV-infected during treatment for hemophilia or other bleeding disorders, or during blood product transfusion or organ transplantation.

cancers was close to the expected (overall RR, 1.1). However, among women (n=134; overall RR, 1.0; 95% CI, 0.9-1.2) the pre- to post-AIDS trend decreased significantly (P for trend=.01), and the RR in the early post-AIDS period was significantly low (n=14; RR, 0.4). In contrast, among men, there was a slight excess of breast cancer (n=9; overall RR, 1.8; 95% CI, 0.8-3.3), particularly among intravenous drug users (n=5; overall RR, 3.9; 95% CI, 1.3-9.2).

Sensitivity Analysis

To assess robustness of our findings, we performed 2 alternative trend tests. The first, likely to be biased toward finding too many positive trends, was based on cancers occurring only in the 2 pre-AIDS periods and the AIDS period. For the majority of the more than 60 different cancer categories studied, trend results were reassuringly similar. In this alternative trend test, the only differences were that lip cancer lost formal statistical significance (P for trend=.19), while trends for anal squamous cell carcinoma (P for trend=.01) and tongue cancer (P for trend=.007) achieved statistical significance. In the second sensitivity analysis, we divided the time window around AIDS into 6 new intervals. Trend results were also essentially unchanged in this analysis. No new sites emerged as potentially influenced by immunosuppression, but the trend test for penile cancer, significant in the original trend analysis, now failed to reach statistical significance (P for trend=.08).

COMMENT

PWAs in the United States are at considerably increased cancer risk compared with the general population. However, of all cancers observed in the period from 60 months before to 27 months after AIDS onset, most (87%) were those already considered as AIDS-defining cancers, notably KS and NHL.²

Our RR estimates for KS (RR, 177.7) and NHL (RR, 72.8) in the early post-AIDS period are lower than estimates from the early HIV epidemic,¹⁴ partly because we used contemporaneous incidence rates (which include KS and NHL

cases among PWAs) to calculate expected numbers. Also, the risk composition of the HIV/AIDS population has changed. The highest RRs for KS were seen in homosexual men and among women who were HIV-infected through sexual contact with a bisexual man, probably reflecting the concurrent epidemics of HIV and human herpesvirus 8, the viral cause of KS, among homosexual/bisexual men.¹⁵ The use of highly active antiretroviral therapy¹⁶ cannot have affected our findings for KS and NHL substantially, as the coverage period in our study ended in 1996.

The PWAs had an excess of a number of cancers without established links to immunosuppression. Some of these cancers have been linked etiologically to HIV-unrelated exposures that are common among PWAs, including cancers of lung and lip, which are considered smoking-related,^{17,18} and penile cancer, which may be related to infection with human papillomavirus.¹⁹

It is difficult to determine if, and to what extent, moderate excesses of non-AIDS-defining cancers are associated with immunosuppression. We used 3 statistical criteria to assist in this process, but none of the criteria, alone or in combination, can determine whether immunosuppression truly plays a causal role. Our findings must be evaluated in the context of other contributing or conflicting evidence. Causality criteria include strength of association, dose-response gradient, specificity, consistency with previous studies, and analogies to other states of immunosuppression.^{20,21} Our overall RR estimates measured the strength of the association between HIV/AIDS-related immunosuppression and cancer risk. The RR in the early post-AIDS period and the trend test served as indicators of a possible dose-response gradient, assuming parallelism between AIDS-relative time and level of immunosuppression. By demanding statistical significance for each of these 3 measures, the list of cancers studied was reduced to a handful deserving further attention.

The non-AIDS-defining cancer most likely to be genuinely associated with

declining immunity is Hodgkin disease. This type of lymphoma was 11.5-fold elevated overall and met our 3 criteria for potential association with immunosuppression in all major strata of sex, race, and HIV exposure. Moreover, our findings are consistent with several smaller studies.^{1,6-8,22-25} As summarized previously,¹ the most frequent Hodgkin disease subtype among PWAs was mixed cellularity. Epstein-Barr virus DNA is detectable in high proportions of HIV/AIDS- and transplantation-associated Hodgkin disease.^{26,27} AIDS-associated NHLs are also more often Epstein-Barr virus-positive than non-AIDS-associated NHLs,²⁸ and most cases of both Hodgkin disease and NHL appear to develop from transformed B-lymphocytes.²⁹ We hypothesize that the Epstein-Barr virus-associated subsets of Hodgkin disease may be associated with immune dysfunction through mechanisms similar to those underlying the established association with NHL.

Our findings for lip cancer are also characterized by consistency with other studies, dose-response relationship with level of immunity (as measured by AIDS-relative time), and analogies to other immunosuppressed states. Our observation of a steady increase in the RR in relation to onset of AIDS adds weight to the 5-fold risk observed by Grulich et al.⁸ The lip cancer excess was not restricted to any 1 HIV risk group in men, and the lack of an association in female PWAs could well be due to limited statistical power. Lip cancer risk has been found to be increased in organ transplant recipients^{30,31} and patients treated with immunosuppressive drugs.³² Squamous cell carcinoma of the skin might be similarly influenced by immunosuppression,^{33,34} but reliable non-melanoma skin cancer data are lacking in large-scale prospective studies and in registry studies such as ours.

The role of immunosuppression in testicular cancer remains unclear. Testicular seminoma met all our criteria for potential association with immunosuppression, and the lack of a similar pattern for non-seminoma testicular can-

cers adds specificity to the association. However, the strength of the association (overall RR, 2.0) does not suggest a major impact of declining immunity on seminoma risk. Corroborative evidence from the literature is sparse. Previous studies either failed to find an increased risk of testicular seminoma^{24,25,35} or did not have sufficient power to identify increased risks as statistically significant,^{6,8} except by inclusion of non-testicular seminomas.⁷ We note that the excess of seminomas was seen predominantly in whites and homosexual men. An infectious etiology has been suggested for testicular seminoma,³⁶⁻³⁹ but the putative agent remains elusive.

All our statistical criteria were also met for soft tissue malignancies, lung cancer, and penile cancer, but these cancer excesses are unlikely to be related to immunosuppression. A significant excess of soft tissue malignancies was seen only in homosexual men, the group at highest risk for KS. This, combined with the large proportion of histologically unspecified soft tissue malignancies, suggests a major contribution by inaccurately coded cases of KS. None of the specified types of sarcoma met our trend criterion. The risk for leiomyosarcoma is markedly increased in children with AIDS,^{10,40} but in this study of adult PWAs, the risk was only 2.3-fold increased and the pre- to post-AIDS trend was not statistically significant. Of note, however, the risk for leiomyosarcoma was 17.3-fold elevated among the 15- to 29-year-old PWAs, thus possibly representing a continuation of the even greater leiomyosarcoma risk in 0- to 14-year-old children with AIDS.¹⁰

It is to be expected that PWAs, who smoke more than the general population,⁴¹ have an excess of lung cancers.¹⁷ Small case series have suggested a particular excess of lung adenocarcinomas.^{42,43} In accordance with some^{6,8} but not all studies,^{22,25,35} we observed an excess lung cancer risk in PWAs. However, this excess was neither restricted to nor particularly pronounced for adenocarcinomas. Although we observed a statistically significant pre- to post-

AIDS trend for lung cancer, this trend was only significant in men (despite large numbers of lung cancer in women). The inconspicuous RR in the distant pre-AIDS period (RR, 1.2) may be too low and, consequently, the significant trend for lung cancer may be an artifact. Lung cancers in PWAs carry an especially poor prognosis, with few patients surviving more than a few months.^{42,43} The lung cancer survival estimates we obtained from SEER data and used to derive expected cancers in the pre-AIDS period might have been too optimistic when applied to an HIV-infected population.

As reported previously, cervical cancer^{6,7} and anal cancer⁵ occurred frequently, and vulvar/vaginal and penile cancers also were in significant excess. Of these, only penile cancer met our trend criterion, but our sensitivity analyses suggested that this was not a robust finding. Human papillomavirus-associated malignancies in PWAs are considered in detail elsewhere.⁹

Breast cancer was the only cancer to exhibit a statistically significant pattern of decreasing RRs with AIDS-relative time. This finding is compatible with the suggestion⁴⁴ that physiological immune activity may somehow facilitate breast carcinogenesis and, consequently, that immunosuppression might reduce breast cancer risk.⁴⁵ However, the overall risk for breast cancer was not reduced. It appears that female PWAs have a normal, but redistributed, breast cancer incidence, perhaps resulting from heightened medical attention around the time of AIDS diagnosis. If HIV-mediated immunosuppression were truly protective, we would have expected an overall reduction in breast cancer risk. Although rare, male breast cancer risk was not reduced but, indeed, almost 4-fold increased in non-homosexual intravenous drug-using men. Further detracting from the idea that immunosuppression protects against breast cancer,⁴⁵ a study of 5692 renal transplant patients in Nordic countries found that breast cancer incidence was not reduced.³⁰

Our study confirms prior findings of elevated risks for multiple myeloma,

anal cancer, brain cancer, and conjunctival carcinoma in PWAs in the United States.^{5,7} Grulich et al⁸ also reported an elevated risk of multiple myeloma in a separate linkage analysis. These cancer excesses do not seem associated with HIV-mediated immunosuppression. With our current, substantially larger database, these cancers exhibited no consistent post-AIDS excess, and none showed statistically significant pre- to post-AIDS trends.

This is the first population-based study with sufficient power to examine the general cancer risk among PWAs by sex, race, and HIV risk group. We had considerable statistical power to detect even moderate increases in the risk for the major cancers. However, despite these advantages, certain limitations need consideration. As discussed for lung cancer, we believe that RRs in the distant pre-AIDS period, particularly for cancers with poor survival rates, may be underestimated due to the use of too optimistic population-based survival rates. Also, if cancer treatment in HIV-infected individuals leads to hastened progression from HIV infection to clinical AIDS, this acceleration would tend to move observed cancers from the distant pre-AIDS period to the recent pre-AIDS period and thus produce too low RRs in the distant pre-AIDS period. Such artificial lowering of the starting point for the trend test would increase the likelihood of detecting spurious increasing trends. Reassuringly, however, this potential bias seems not to have had a major impact on our results, since only a handful of cancers met our criteria for potential association with immunosuppression in the original analysis and in the 2 sensitivity analyses.

In summary, PWAs are at increased risk of cancers other than KS, NHL, and cervical cancer. For most cancers, excesses are probably attributable to lifestyle factors among PWAs or to inaccurate recording in cancer registries of the more common AIDS-defining cancers. However, 3 specific types of cancer, notably Hodgkin disease, but possibly also lip cancer and testicular seminoma, may be genuinely influenced by immuno-

suppression. Our finding of clearly increased risks of Hodgkin disease in all groups of PWAs, and a statistically significant pre- to post-AIDS trend, show that the risk of Hodgkin disease increases with advancing immunosuppression and suggest it be considered as an AIDS-defining condition.

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Acquisition of data: Biggar, Goedert.

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Drafting of the manuscript: Frisch, Biggar.

Critical revision of the manuscript for important intellectual content: Frisch, Biggar, Engels, Goedert, *Statistical expertise:* Frisch, Biggar, Engels, Goedert. *Obtained funding:* Biggar, Goedert.

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REFERENCES

1. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 67: Human Immunodeficiency Viruses and Human T-Cell Lymphotropic Viruses. Lyon, France: International Agency for Research on Cancer; 1996.
2. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Morb Mortal Wkly Rep.* 1992;41:1-19.
3. Biggar RJ. Epidemiology of malignancies in HIV/AIDS. In: Feigal EG, Levine AM, Biggar RJ, eds. *AIDS-Related Cancers and Their Treatment.* New York, NY: Marcel Dekker Inc; 2000:25-58.
4. Serraino D. The spectrum of AIDS-associated cancers in Africa. *AIDS.* 1999;13:2589-2590.
5. Melbye M, Cote TR, Kessler L, et al, for the AIDS/Cancer Working Group. High incidence of anal cancer among AIDS patients. *Lancet.* 1994;343:636-639.
6. Franceschi S, Dal Maso L, Armani S, et al, for the Cancer and AIDS Registry Linkage Study. Risk of cancer other than Kaposi's sarcoma and non-Hodgkin's lymphoma in persons with AIDS in Italy. *Br J Cancer.* 1998;78:966-970.
7. Goedert JJ, Cote TR, Virgo P, et al. Spectrum of AIDS-associated malignant disorders. *Lancet.* 1998;351:1833-1839.
8. Grulich AE, Wan X, Law MG, et al. Risk of cancer in people with AIDS. *AIDS.* 1999;13:839-843.
9. Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. *J Natl Cancer Inst.* 2000;92:1500-1510.
10. Biggar RJ, Frisch M, Goedert JJ, for the AIDS-Cancer Match Registry Study Group. Risk of cancer in children with AIDS. *JAMA.* 2000;284:205-209.
11. World Health Organization. *International Classification of Diseases for Oncology.* 2nd ed. Geneva, Switzerland: World Health Organization; 1990.
12. Breslow NE, Day NE. *Statistical Methods in Cancer Research, II: The Design and Analysis of Cohort Studies.* Lyon, France: International Agency for Research on Cancer; 1987. IARC Scientific Publications No. 82.
13. Cox DR, Hinkley DV. *Theoretical Statistics.* London, England: Chapman & Hall; 1974:279-363.
14. Biggar RJ, Rosenberg PS, Cote T, for the Multistate AIDS/Cancer Match Study Group. Kaposi's sarcoma and non-Hodgkin's lymphoma following the diagnosis of AIDS. *Int J Cancer.* 1996;68:754-758.
15. O'Brien TR, Kedes D, Ganem D, et al. Evidence for concurrent epidemics of human herpesvirus 8 and human immunodeficiency virus type 1 in US homosexual men. *J Infect Dis.* 1999;180:1010-1017.
16. International Collaboration on HIV and Cancer. Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults. *J Natl Cancer Inst.* 2000;92:1823-1830.
17. Blot WJ, Fraumeni JF Jr. Cancers of the lung and pleura. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention.* New York, NY: Oxford University Press; 1996:637-665.
18. Blot WJ, McLaughlin JK, Devesa SS, Fraumeni JF Jr. Cancers of the oral cavity and pharynx. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention.* New York, NY: Oxford University Press; 1996:666-680.
19. Gregoire L, Cubilla AL, Reuter VE, et al. Preferential association of human papillomavirus with high-grade histologic variants of penile-invasive squamous cell carcinoma. *J Natl Cancer Inst.* 1995;87:1705-1709.
20. Rothman KJ. Causation and causal inference. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention.* New York, NY: Oxford University Press; 1996:3-10.
21. Hill AB. The environment and disease: association or causation? *Proc R Soc Med.* 1965;58:295-300.
22. Cookley CD, Hwang LY, Waller DK, Ford CE. HIV-related malignancies: community-based study using linkage of cancer registry and HIV registry data. *Int J STD AIDS.* 1999;10:795-802.
23. Hessel NA, Katz MH, Liu JY, et al. Increased incidence of Hodgkin disease in homosexual men with HIV infection. *Ann Intern Med.* 1992;117:309-311.
24. Petrukevitch A, Del Amo J, Phillips AN, et al, for the London African HIV/AIDS Study Group. Risk of cancer in patients with HIV disease. *Int J STD AIDS.* 1999;10:38-42.
25. Reynolds P, Saunders LD, Layefsky ME, Lemp GF. The spectrum of acquired immunodeficiency syndrome (AIDS)-associated malignancies in San Francisco, 1980-1987. *Am J Epidemiol.* 1993;137:19-30.
26. Mueller NE. Hodgkin's disease. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention.* New York, NY: Oxford University Press; 1996:893-919.
27. Rowlings PA, Curtis RE, Passweg JR, et al. Increased incidence of Hodgkin's disease after allogeneic bone marrow transplantation. *J Clin Oncol.* 1999;17:3122-3127.
28. Mueller N. Overview of the epidemiology of malignancy in immune deficiency. *J Acquir Immune Defic Syndr.* 1999;21(suppl 1):S5-S10.
29. Brüninger A, Hansmann ML, Strickler JG, et al. Identification of common germinal-center B-cell precursors in two patients with both Hodgkin's disease and non-Hodgkin's lymphoma. *N Engl J Med.* 1999;340:1239-1247.
30. Birkeland SA, Storm HH, Lamm LU, et al. Cancer risk after renal transplantation in the Nordic countries, 1964-1986. *Int J Cancer.* 1995;60:183-189.
31. Penn I. Cancer is a complication of severe immunosuppression. *Surg Gynecol Obstet.* 1986;162:603-610.
32. Brennan P, Coates M, Armstrong B, et al. Second primary neoplasms following non-Hodgkin's lymphoma in New South Wales, Australia. *Br J Cancer.* 2000;82:1344-1347.
33. Gupta AK, Cardella CJ, Haberman HF. Cutaneous malignant neoplasms in patients with renal transplants. *Arch Dermatol.* 1986;122:1288-1293.
34. Maurer TA, Christian KV, Kerschmann RL, et al. Cutaneous squamous cell carcinoma in human immunodeficiency virus-infected patients. *Arch Dermatol.* 1997;133:577-583.
35. Koblin BA, Hessel NA, Zauber AG, et al. Increased incidence of cancer among homosexual men, New York City and San Francisco, 1978-1990. *Am J Epidemiol.* 1996;144:916-923.
36. Shimakage M, Oka T, Shinka T, et al. Involvement of Epstein-Barr virus expression in testicular tumors. *J Urol.* 1996;156:253-257.
37. Gray A, Guillou L, Zufferey J, et al. Persistence of parvovirus B19 DNA in testis of patients with testicular germ cell tumours. *J Gen Virol.* 1998;79(pt 3):573-579.
38. Akre O, Lipworth L, Tretli S, et al. Epstein-Barr virus and cytomegalovirus in relation to testicular-cancer risk. *Int J Cancer.* 1999;82:1-5.
39. Goedert JJ, Sauter ME, Jacobson LP, et al. High prevalence of antibodies against HERV-K10 in patients with testicular cancer but not with AIDS. *Cancer Epidemiol Biomarkers Prev.* 1999;8:293-296.
40. Granovsky MO, Mueller BU, Nicholson HS, et al. Cancer in human immunodeficiency virus-infected children. *J Clin Oncol.* 1998;16:1729-1735.
41. Stall RD, Greenwood GL, Acree M, et al. Cigarette smoking among gay and bisexual men. *Am J Public Health.* 1999;89:1875-1878.
42. Karp J, Profeta G, Marantz PR, Karpel JP. Lung cancer in patients with immunodeficiency syndrome. *Chest.* 1993;103:410-413.
43. Tirelli U, Spina M, Sandri S, et al, for the Italian Cooperative Group on AIDS and Tumors. Lung carcinoma in 36 patients with human immunodeficiency virus infection. *Cancer.* 2000;88:563-569.
44. Stewart T, Tsai SC, Grayson H, et al. Incidence of de-novo breast cancer in women chronically immunosuppressed after organ transplantation. *Lancet.* 1995;346:796-798.
45. Stewart TH, Sage RD, Stewart AF, Cameron DW. Breast cancer incidence highest in the range of one species of house mouse, *Mus domesticus.* *Br J Cancer.* 2000;82:446-451.