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Increased risk of histologically-defined cancer subtypes in HIV-infected individuals: clues for possible immunosuppression-related or infectious etiology

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Abstract

Background—Malignancies that occur in excess among HIV-infected individuals may be caused by immunosuppression or infections. Because histologically-defined cancer subtypes have not been systematically evaluated, we assessed their risk among people with AIDS.

Methods—Analyses included 569,268 people with AIDS from the HIV/AIDS Cancer Match Study, a linkage of 15 U.S. population-based HIV/AIDS and cancer registries during 1980–2007. Standardized incidence ratios (SIRs) were estimated to compare cancer risk in people with AIDS to the general population overall, and stratified by age, calendar period (a proxy of changing HIV therapies) and time since AIDS (a proxy of immunosuppression).

Results—Sixteen individual cancer histologies or histology groupings manifested significantly elevated SIRs. Risks were most elevated for adult T-cell leukemia/lymphoma (SIR=11.3), neoplasms of histiocytes and accessory lymphoid cells (SIR=10.7), giant cell carcinoma (SIR=7.51) and leukemia not otherwise specified (NOS) (SIR=6.69). SIRs ranged from 1.4 to 4.6 for spindle cell carcinoma, bronchioloalveolar adenocarcinoma, adnexal and skin appendage neoplasms, sarcoma NOS, spindle cell sarcoma, leiomyosarcoma, mesothelioma, germ cell tumors, plasma cell tumors, immunoproliferative diseases, acute lymphocytic leukemia and myeloid leukemias. For several of these cancer subtypes, we observed significant declines in SIRs across calendar periods (consistent with decreasing risk with improved HIV therapies) or increase in SIRs with time since AIDS (i.e., prolonged immunosuppression).

Conclusions—The elevated risk of certain cancer subtypes in people with AIDS may point to an etiologic role of immunosuppression or infection. Future studies are needed to further investigate these associations and evaluate candidate infectious agents.

Keywords

HIV; immunosuppression; infection; cancer

Introduction

HIV-infected individuals have an increased risk of developing a number of cancers compared to the general population (1;2). In particular, the risk of cancers with infectious

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etiologies far exceeds the risk in the general population, due to HIV-induced immune suppression and an increased prevalence of some oncogenic infections (1).

Indeed, these elevated risks have provided important clues to cancer etiology. For example, people with AIDS had a 53,000-fold increased risk of KS compared to the general population at the beginning of the AIDS epidemic (2). This observation led to the hypothesis that KS may be caused by a virus, which subsequently resulted in the discovery of KS-associated herpesvirus (KSHV) in 1994 (4). More recently, HIV was reported to be associated with a 13-fold increase in the risk of Merkel cell carcinoma (5), a rare type of skin cancer. This elevation suggested a potential infectious etiology and led to the 2008 discovery of Merkel cell polyomavirus, the possible agent of Merkel cell carcinoma (6). In addition, HIV is associated with a 77-fold elevated risk of non-Hodgkin lymphoma and an 11-fold elevated risk of Hodgkin lymphoma (both caused by Epstein-Barr virus [EBV]), a 5-fold elevated risk of liver cancer (caused by hepatitis B virus [HBV] and hepatitis C virus [HCV]), and a 6-fold elevated risk of cervical cancer and 29-fold elevated risk of anal cancer (both caused by human papillomavirus [HPV]) (1–3).

Previous work describing the risk of malignancies among HIV-infected individuals has commonly grouped cancers based on the primary site (1;2;7). It is increasingly recognized that within a given cancer site, there is etiologic heterogeneity, and that risk factors may differ across histologic subtypes. Though HIV does not increase the risk of most common cancers, these broad classifications may mask associations between HIV and less common cancer entities. Cancers that may have been missed could plausibly correspond to unique histologic subtypes that can be diagnosed across multiple anatomic sites, or rare entities that would not contribute substantially to overall risk at a site. In the current study, we therefore evaluated the risk of individual histologic subtypes of cancer in people with AIDS, relative to the general population. A potential etiologic role of immunosuppression or infection may be indicated for such malignancies if they occur in excess among HIV-infected individuals.

Methods

Our analyses used data from the HIV/AIDS Cancer Match (HACM) Study, a linkage of population-based HIV/AIDS and cancer registries in 15 U.S. areas (additional information at www.hivmatch.cancer.gov) (8). A probabilistic algorithm was used to match records based on name, Social Security number, sex, birth date, death date, and race (8). Only anonymized data were retained by investigators. The study was approved by institutional review boards at each participating registry.

International Classification of Diseases for Oncology (ICD-O-3) topography and histology codes were used to classify cancers (9). We identified individual histologic subtypes of cancer that may occur more frequently in people with AIDS than in the general population by estimating the proportion of cases in HACM cancer registries that matched to AIDS registries. We estimated the proportion of cancer cases with AIDS for 659 histology codes. Each individual histology code where ≥1% of cancer registry cases matched to the AIDS registry in any of three age groups (0–19, 20–49 and 50+ year olds) was identified for further analyses. Upon review of the initial results, we collapsed related histology codes into categories, and identified histology categories where ≥1% of cases matched to the AIDS registry. For example, the category “immunoproliferative disease” includes immunoproliferative diseases, not otherwise specified (NOS; ICD-O3 code 9760), Waldenström macroglobulinemia (9761) and heavy chain disease, NOS (9762). We excluded histologies that are classified by the Centers for Disease Control and Prevention as AIDS-defining cancers (e.g., KS, Burkitt lymphoma) (10), or have well-established associations with HIV infection (e.g., Hodgkin lymphoma, hepatocellular carcinoma).

To assess the risk of each histologic subtype of interest in people with AIDS relative to the general population, we estimated standardized incidence ratios (SIRs). This analysis included people with AIDS who contributed follow-up from the start of registry coverage or 60 months prior to AIDS onset (whichever occurred later) to the earliest of death, end of complete registry coverage or 120 months after AIDS onset. Cancers diagnosed during 1980–2007 were identified from the cancer registries. SIRs were calculated as the number of observed cases among people with AIDS divided by the number of expected cases, where expected cases were based on rates from cancer registry data and standardized by age, sex, race, calendar year and registry to the AIDS population. Expected counts corresponding to prevalent cancers occurring before or at AIDS were adjusted for survival bias.

We then focused on malignancies for which the SIR was significantly elevated ($p<0.05$) and there were at least 5 cases among people with AIDS. We estimated SIRs stratified by attained age group (0–14, 15–29, 30–49 and 50+ years old), time relative to AIDS onset (−60 to −25, −24 to −7, −6 to +3, +4 to +27, +28 to +60 and +61 to +120 months), and attained calendar period (1980–1989 [no antiretroviral therapy era], 1990–1995 [some antiretroviral therapy era], 1996–2000 [early highly active antiretroviral therapy (HAART) era], 2001–2007 [late HAART era]). Tests for trend in SIRs across strata were assessed with Poisson regression. Examining patterns of elevated cancer risk across calendar periods and time since AIDS diagnosis may further support the role of immune suppression or co-infections. Decreasing risk over calendar time suggests that immune reconstitution (i.e., HAART) reduces cancer risk, and increasing risk with time since AIDS suggests that advanced immune suppression increases cancer risk. The period 6 months before to 3 months after AIDS onset was excluded from the trend test for time relative to AIDS onset, because increased medical surveillance inflates cancer rates during this time period (11).

All statistical tests were two-sided. P-values≤0.05 were considered to be statistically significant.

Results

The HACM Study includes 569,268 people with AIDS who contributed follow-up during 1980–2007. Subjects were primarily male (80.2%) with an equal proportion of non-Hispanic whites (38.4%) and non-Hispanic blacks (40.5%), and fewer Hispanics (21.1%). The median age at AIDS was 37 years. The most common HIV transmission risk group was men who have sex with men (MSM) (43.6%), followed by injection drug users (IDUs) (24.4%), and MSM/IDUs (5.8%); people with other or unspecified risk groups comprised 26.2% of the population.

The vast majority of the 659 individual histology codes examined were not identified as having an AIDS prevalence of ≥1% in the first phase of our study, including many common histologies, such as infiltrating duct carcinoma, renal cell carcinoma and malignant melanoma. However, based on our search approach, we identified 16 individual histologic subtypes or histology groupings where SIRs were significantly elevated in people with AIDS (Table 1). The most common of these cancers were germ cell tumors (n=340), plasma cell tumors (n=290) and myeloid leukemias (n=283). The majority of giant cell carcinomas (92.9%), spindle cell carcinomas (54.5%) and bronchioloalveolar adenocarcinomas (96.6%) occurred in the lung. Germ cell tumors primarily occurred in the testes (91.8%), 97.2% of plasma cell tumors were multiple myeloma, and 66.7% of immunoproliferative disease cases were Waldenström macroglobulinemia.

Of those cancers presented in Table 1, risks were most elevated for adult T-cell leukemia/lymphoma (SIR=11.3), neoplasms of histiocytes and accessory lymphoid cells (SIR=10.7),

giant cell carcinoma (SIR=7.51) and leukemia NOS (SIR=6.69). SIRs ranged from 1.4 to 4.6 for spindle cell carcinoma, bronchioloalveolar adenocarcinoma, adnexal and skin appendage neoplasms, sarcoma NOS, spindle cell sarcoma, leiomyosarcoma, mesothelioma, germ cell tumors, plasma cell tumors, immunoproliferative diseases, acute lymphocytic leukemia and myeloid leukemias.

SIRs for the most frequent histologies or primary sites were examined for selected cancers (Table 1). Neoplasms of histiocytes and accessory lymphoid cells included two histologies with strong associations with AIDS: malignant histiocytosis (SIR=12.5) and histiocytic sarcoma (SIR=24.5). Risk was strongly elevated for some histologic entities localized to the lung: giant cell carcinomas (SIR=8.35), spindle cell sarcomas (SIR=12.3) and spindle cell carcinomas (SIR=8.63). Among germ cell tumors, risk was significantly elevated for testes seminoma (SIR=1.44), but not testes non-seminoma (SIR=1.14). Additionally, the elevated risk of adnexal and skin appendage neoplasms in people with AIDS was largely driven by sebaceous adenocarcinomas (SIR=7.50). Risk varied among myeloid leukemias, with the most common subtypes being acute myeloid leukemia (SIR=2.41), chronic myeloid leukemia (SIR=0.82), acute myelomonocytic leukemia (SIR=3.75) and myelodysplastic syndrome (SIR=5.28).

A significant decline in SIR was observed with increasing age for leiomyosarcoma (p-trend<0.0001), with the highest SIR in children 0–14 years old (n=8; SIR=540; 95% CI 230–1100). SIRs also declined with age for bronchioloalveolar adenocarcinoma (p-trend=0.0009), sarcoma NOS (p-trend=0.01), plasma cell tumors (p-trend<0.0001), leukemia NOS (p-trend=0.002), adult T-cell leukemia/lymphoma (p-trend=0.02) and myeloid leukemias (p-trend=0.02); no cases of these malignancies were observed in 0–14 year olds, but the highest SIRs occurred among 15–29 year olds.

Significant declines were observed across calendar periods for some cancers, with the highest SIRs in the pre-HAART eras (i.e., 1980–1989 and 1990–1995). Figure 1 presents SIRs for cancers with statistically significant trends: bronchioloalveolar adenocarcinoma (p-trend=0.02), sarcoma NOS (p-trend=0.0003), plasma cell tumors (p-trend=0.0001), neoplasms of histiocytes and accessory lymphoid cells (p-trend=0.05), leukemia NOS (p-trend=0.02) and adult T-cell leukemia/lymphoma (p-trend=0.01).

Figure 2 presents SIRs for cancers with statistically significant trends in time relative to AIDS onset. SIRs for spindle cell sarcoma (p-trend=0.03) and leiomyosarcoma (p-trend=0.008) increased with increasing time since AIDS onset. In contrast, SIRs for plasma cell tumors decreased with increasing time since AIDS (p-trend=0.003).

Discussion

We identified 16 histologically-defined cancers, characterized as individual histologic subtypes or histology groups that were significantly elevated in people with AIDS compared to the general population. These diverse malignancies, many of which are uncommon, include specific carcinomas, sarcomas and hematological malignancies, as well as germ cell and plasma cell tumors. The risks of some of these malignancies have been shown to be elevated in HIV-infected individuals in previous studies (2;3;12–16), while the occurrence of others has not been evaluated previously. The increased risk of these cancers among people with AIDS supports an etiologic role of immune suppression or infection. As we discuss further below, additional considerations in weighing this possibility include the magnitude of the increased risk; changes in cancer risk with advanced HIV infection or introduction of effective HIV therapy; and other available biological, clinical, or epidemiologic data.

Two of these cancers, leiomyosarcoma and adult T-cell leukemia/lymphoma, have been previously linked to infection with EBV (17) and human T-lymphotropic virus 1 (HTLV-1) (18), respectively. In our study, leiomyosarcoma risk was elevated two-fold overall, but more than 500-fold in children aged 0–14 years old, compared to the general population. Previous studies have described this increased risk in children (12), and have shown that, in contrast to leiomyosarcomas in HIV-uninfected individuals, those arising in HIV-infected individuals are largely EBV-positive (17). SIRs for leiomyosarcoma increased with time since AIDS, suggesting that prolonged immune suppression increases leiomyosarcoma risk. The risk of adult T-cell leukemia/lymphoma, which is caused by infection with HTLV-1 (18), was strongly elevated in the AIDS population, as observed previously (13). Risk declined over calendar time, indicating a potential protective effect related to HAART. However, the excess risk of T-cell leukemia/lymphoma may also be due to misclassification of B-cell lymphomas, which are known to be strongly associated with HIV infection.

Infectious etiologies have not been established for the remaining cancers identified in our study. Though it has been suggested that infection with simian virus 40, which contaminated some polio vaccines in the 1950s and 1960s, may be associated with the development of mesothelioma, the most recent laboratory and epidemiologic studies have not supported this hypothesis (19;20). Further, mumps virus, EBV, HPV, cytomegalovirus and parvovirus B19 have each been suggested, but not established, as potentially associated with germ cell tumors of the testes (14;21;22). As we report here, people with AIDS have an elevated risk for testicular seminoma (14). Associations with HCV and HBV have been reported for immunoproliferative diseases and, in particular, Waldenström macroglobulinemia (23;24).

Prior studies have shown an increased risk of multiple myeloma in HIV-infected individuals and immunosuppressed transplant recipients (3). Case reports describe detection of EBV in tumor cells from immunosuppressed multiple myeloma cases (25), and one case-control study found an association with HBV (26). However, other studies have shown no associations with these viruses (23;27). While the declining risk of plasma cell tumors over time suggests that HAART may reduce the risk of these cancers, the decrease in risk following AIDS onset is difficult to explain. Risk of appendageal carcinomas has previously been shown to be elevated in people with AIDS (16) and possibly transplant recipients (28). Neoplasms of histiocytes and accessory lymphoid cells include malignant histiocytosis and histiocytic sarcoma. These rare malignancies are strongly elevated in people with AIDS. Some case reports have described detection of EBV in these tumors (29;30), and a possible role of immunosuppression is supported by our observation of a decline in risk over calendar time.

HIV-infected people have an elevated risk of developing lung cancer, even after accounting for a high prevalence of tobacco use (15). We identified three uncommon cancer subtypes occurring primarily in the lung where risk was elevated in people with AIDS. Ninety-three percent of giant cell carcinomas, 55% of spindle cell carcinomas and 97% of bronchioloalveolar adenocarcinomas identified in this study occurred in the lung. These histologic subtypes of lung cancer vary in their behavior and associations with cigarette smoking. Giant cell and spindle cell carcinomas of the lung are classified as sarcomatoid carcinomas and comprise 0.3–1.3% of all lung malignancies (31). More than 90% of sarcomatoid carcinomas occur in heavy smokers (31). Given the rarity of these malignancies, it is possible that some may be misclassified cases of pulmonary KS. Bronchioloalveolar adenocarcinoma occurs along alveolar structures of the lung without pleural, vascular or stromal invasion, and is more weakly associated with tobacco smoking (32). HAART may reduce the risk of bronchioloalveolar adenocarcinoma in HIV-infected individuals, as the relative risk in people with AIDS declined over time. Though a high prevalence of smoking in HIV-infected individuals may be driving the elevated risk of these

three cancer histologies, it is possible that HIV-related immune disturbance, pulmonary inflammation, or lung infections also contribute (33).

Finally, we identified several additional sarcomas and hematological malignancies that occur at increased frequency in people with AIDS. The risks of two poorly specified types of sarcoma (i.e., sarcoma NOS and spindle cell sarcoma) were elevated 17-fold and 5-fold, respectively in people with AIDS. The elevated risk of sarcoma NOS, which was most pronounced in MSM, probably reflects poorly classified KS cases. Spindle cell sarcoma may also reflect misclassified KS or possibly leiomyosarcoma (34). Consistent with previous studies that have shown an increased risk of broadly grouped lymphomas and leukemias in HIV-infected individuals (2;3), we found elevations for acute lymphocytic leukemia and myeloid leukemia.

The main strength of our analysis was the use of data from the HACM Study, which includes 569,268 people with AIDS followed over the duration of the AIDS epidemic. Due to the large number of people with AIDS, we were able to examine the risk of specific histologic subtypes and less common malignancies, which have not been previously assessed and would be impossible to evaluate in a smaller sample. As the analyses presented here were exploratory, the results should be interpreted with caution. We examined (but did not present) a large number of associations with largely null results, and did not correct for multiple comparisons. Nonetheless, the purpose of this study was to generate hypotheses and identify potentially intriguing areas for future research.

In conclusion, people with AIDS are at an increased risk of developing a number of histologically-defined malignancies. Many of these malignances are rare and lack strong *a priori* evidence for a potential role for infection or immune suppression. Nonetheless, the markedly increased risk for some of these entities is striking, and in the absence of other compelling explanations, it may be productive to further investigate these associations and evaluate candidate infectious agents.

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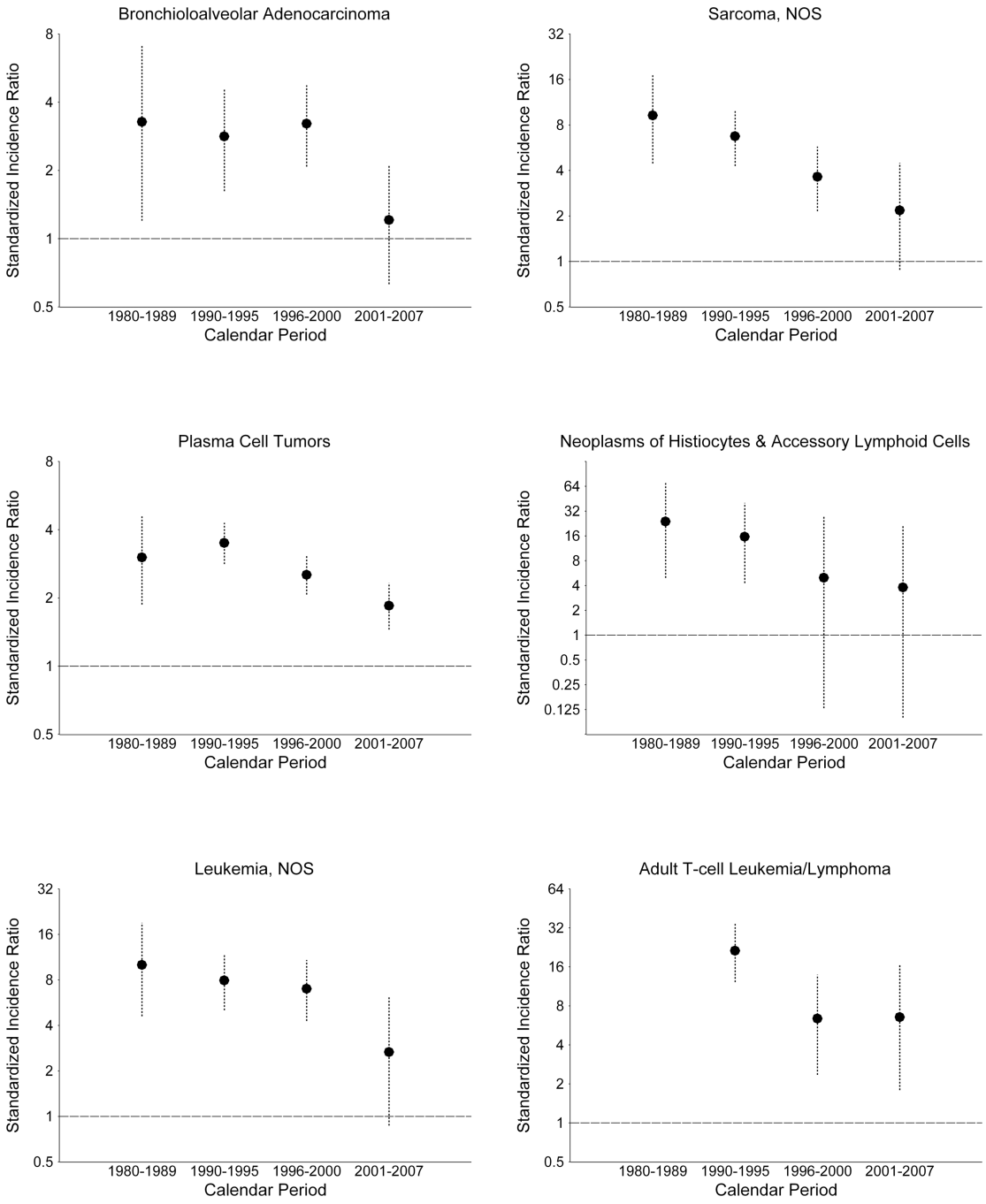

Figure 1.

Standardized incidence ratios (SIRs) comparing risk of cancer in people with AIDS to the general population by calendar period. Points indicate SIRs and vertical lines indicate 95% confidence intervals. P-trend values are as follows: bronchioloalveolar adenocarcinoma (p-trend=0.02), sarcoma NOS (p-trend=0.0003), plasma cell tumors (p-trend=0.0001), neoplasms of histiocytes and accessory lymphoid cells (p-trend=0.05), leukemia NOS (p-trend=0.02) and adult T-cell leukemia/lymphoma (p-trend=0.01). Zero cases of adult T-cell leukemia/lymphoma occurred in people with AIDS during 1980–1989.

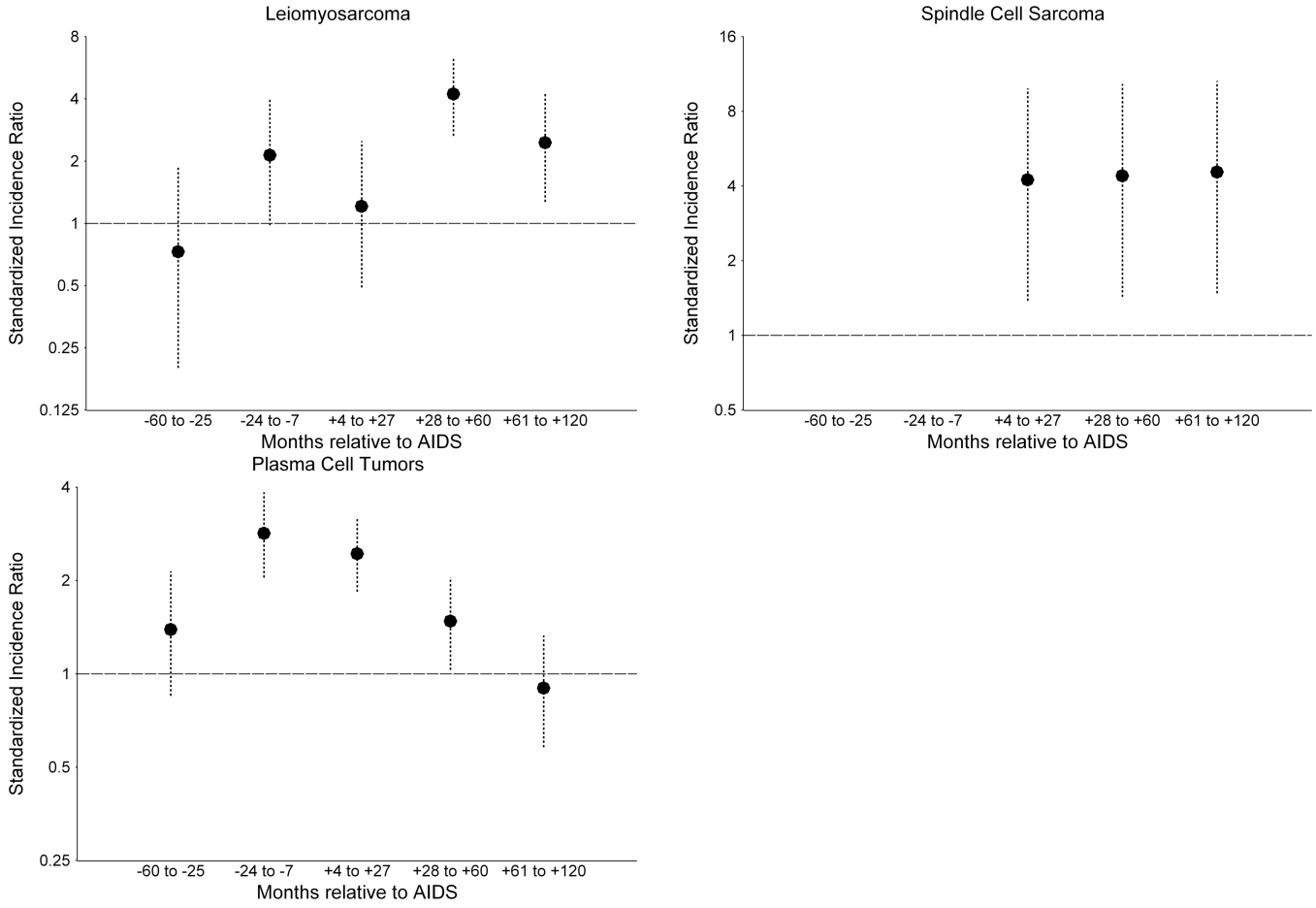

Figure 2.

Standardized incidence ratios (SIRs) comparing risk of cancer in people with AIDS to the general population by time relative to AIDS onset. Points indicate SIRs and vertical lines indicate 95% confidence intervals. P-trend values are as follows: spindle cell sarcoma (p-trend=0.03), leiomyosarcoma (p-trend=0.006) and plasma cell tumors (p-trend=0.003). Zero cases of spindle cell sarcoma occurred in the period 60 months to 25 months before AIDS and the period 24 to 7 months before AIDS. The period 6 months before to 3 months after AIDS onset was excluded from the trend test, because increased medical surveillance at the time of AIDS diagnosis inflates cancer risk estimates during this time period.

Table 1

Standardized incidence ratios for histologic subtypes of cancer among people with AIDS, 1980–2007.

Cancer histology type (ICD-O-3 codes)	N	SIR	95% CI
Adult T-cell leukemia/lymphoma (HTLV-1 positive) (9827)	26	11.3	7.38-16.6
Neoplasms of histiocytes and accessory lymphoid cells (9750–9759)	9	10.7	4.88-20.2
Malignant histiocytosis (9750)	*4*	*12.5*	*3.42-3.21*
Histiocytic sarcoma (9755)	*5*	*24.5*	*7.96-57.2*
Giant cell carcinoma (8031)	14	7.51	4.11-12.6
Lung and bronchus	*13*	*8.35*	*4.45-14.3*
Leukemia, not otherwise specified (9800–9809)	57	6.69	5.07-8.67
Sarcoma, not otherwise specified (8800)	58	4.59	3.48-5.93
Soft tissue including heart	*23*	*3.24*	*2.05-4.86*
Spindle cell carcinoma (8032)	11	4.12	2.06-7.37
Lung and bronchus	*6*	*8.63*	*3.17-18.8*
Immunoproliferative diseases (9760–9769)	15	3.84	2.15-6.34
Waldenstrom macroglobulinemia (9761)	*10*	*2.72*	*1.30-4.99*
Adnexal and skin appendage neoplasms (8390–8420)	23	3.26	2.07-4.89
Sebaceous adenocarcinoma (8410)	*13*	*7.50*	*3.99-12.8*
Acute lymphocytic leukemia (9830–9839, 9828)	69	3.13	2.43-3.96
Precursor cell lymphoblastic leukemia (9835)	*68*	*3.61*	*2.80-4.57*
Spindle cell sarcoma (8801)	16	3.00	1.71-4.87
Soft tissue including heart	*5*	*1.63*	*0.53-3.81*
Lung and bronchus	*4*	*12.3*	*3.36-31.5*
Plasma cell tumors (9730–9739)	290	2.55	2.26-2.86
Multiple myeloma (9731-9732, 9734)	*282*	*2.49*	*2.21-2.80*
Bronchioloalveolar adenocarcinoma (8250–8255)	59	2.34	1.78-3.02
Lung and bronchus	*57*	*2.58*	*1.95-3.34*
Leiomyosarcoma (8890)	66	2.32	1.80-2.95
Myeloid leukemias (9840–9999)	283	1.98	1.76-2.23
Acute myeloid leukeimia (9861)	*92*	*2.41*	*1.95-2.96*
Chronic myeloid leukemia, NOS (9863)	*32*	*0.82*	*0.56-1.15*
Acute myelomonocytic leukemia (9867)	*20*	*3.75*	*2.29-5.80*
Myelodysplastic syndrome, NOS (9989)	*28*	*5.28*	*3.51-7.64*
Mesothelioma (9050–9059)	22	1.84	1.15-2.78
Germ cell tumors (9060–9089)	340	1.40	1.26-1.56
Testes seminoma (9060–9063)	*220*	*1.44*	*1.26-1.65*
Testes non-seminoma	*92*	*1.18*	*0.95-1.44*

Abbreviations: AIDS: Acquired Immune Deficiency Syndrome, SIR: standardized incidence ratio, CI: confidence interval, ICD-O-3: International Classification of Diseases for Oncology, HTLV-1: human T-lymphotropic virus 1