Cancers associated with Kaposi’s sarcoma (KS) in AIDS: a link between KS herpesvirus and immunoblastic lymphoma

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Summary Kaposi’s sarcoma (KS), common among persons with acquired immunodeficiency syndrome (AIDS), is caused by KS herpesvirus (KSHV) but whether KSHV causes other malignancies is uncertain. Using linked United States AIDS and cancer registries, we measured the incidence of specific malignancies in persons with AIDS (4–27 months after AIDS onset). We identified associations with KSHV by calculating a relative risk: cancer incidence in persons with KS (all were KSHV-infected) divided by incidence in persons without KS. Using Poisson regression, relative risks were adjusted for human immunodeficiency virus risk group, gender, age, race, and calendar year. We included 189 159 subjects (26 972 with KS). Immunoblastic lymphoma was significantly associated with KS (506 cases; relative risks: unadjusted 2.44, 95%CI 2.00–2.96, adjusted 1.58, 95%CI 1.29–1.93). Only one immunoblastic lymphoma had pleura as primary site. None of 37 other specified malignancies (other non-Hodgkin lymphomas, haematological malignancies, solid tumours) was significantly associated with KS. In summary, the association of immunoblastic lymphoma with KS was specific among examined malignancies and remained significant after statistical adjustment. Our findings, and the previously demonstrated presence of KSHV in the histologically related primary effusion lymphoma, suggest that KSHV is involved in the pathogenesis of some immunoblastic lymphomas. © 2001 Cancer Research Campaign

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Kaposi’s sarcoma herpesvirus (KSHV), also known as human herpesvirus 8, is now established as the aetiologic agent of Kaposi’s sarcoma (KS) (Antman and Chang, 2000). Most KSHV-infected people are asymptomatic. However, with immunosuppression induced by human immunodeficiency virus type 1 (HIV), risk for KS increases substantially (Martin et al, 1998).

Several lines of evidence suggest that KSHV is also a cause of lymphoma in HIV-infected persons. KSHV is found within circulating B lymphocytes (Blackbourn et al, 1997) and is closely related to Epstein–Barr virus and herpesvirus saimiri, which each cause lymphoma (International Agency for Research on Cancer, 1997, p. 375–494). KSHV might stimulate lymphocytes to proliferate abnormally through virally encoded homologues of cytokines, such as v-interleukin 6, or proteins that interfere with cell cycle control, such as v-cyclin or latent nuclear antigen (Moore et al, 1996; Radkov et al, 2000). KSHV is consistently detected in acquired immunodeficiency syndrome (AIDS)-associated primary effusion lymphoma, a rare tumour arising from pleura, pericardium or peritoneum (Cesarman et al, 1995; Nador et al, 1996; Gessain et al, 1997). The virus is also found in lymphomas occurring in multicentric Castleman’s disease (Dupin et al, 2000). Nonetheless, it remains uncertain whether KSHV actually causes these lymphomas or other lymphoma variants among persons with AIDS.

There are few systematic data on the relationship between KSHV and various malignancies, including lymphoma. In the present study, we compared the incidence of various malignancies in persons with AIDS-associated KS (all of whom were KSHV-infected) with the incidence in other persons with AIDS (most of whom were KSHV-uninfected). With this design, a significant association with KS served to identify tumours for which KSHV might be aetiologic. An advantage of our registry-based study was its large size, including over 189 000 persons with AIDS.

MATERIALS AND METHODS

Study subjects and matching

We used data from the AIDS-Cancer Match Registry study. As described elsewhere (Frisch et al, 2001), this study provides data on cancer incidence in persons with AIDS, through linkage of cancer and AIDS registries from eleven areas of the United States, namely, the states of Connecticut, Florida, Illinois, Massachusetts, New Jersey, and New York, and the metropolitan areas of Atlanta, Los Angeles, San Diego, San Francisco, and Seattle. Thus, included subjects were those persons with an AIDS diagnosis (as documented in an AIDS registry) occurring in the period of registration covered by the relevant cancer registry, and the occurrence of malignancies in these subjects was identified using the cancer registries. The period of registration varied by cancer registry, but all included 1983–1994, except San Diego, where registration began in 1988, and no data were available after 1996. In the present study, 2 areas were excluded, because the cancer registry
included a substantial number of inaccurately diagnosed cases of KS or provided data only on first malignancies.

All subjects were classified according to whether they developed KS at any point during observation, based on diagnoses recorded in either AIDS or cancer registries. For this purpose, we considered cases of KS dated from AIDS onset (under the definition of AIDS, no cases of KS occurred before AIDS) until 60 months after AIDS onset.

### Incidence of malignancies

Using diagnoses recorded in the cancer registries, we calculated the incidence of various malignancies from 4 to 27 months after AIDS onset (post-AIDS period). This 2-year period excluded the 3 months immediately following AIDS (AIDS period), since cancer ascertainment would have been elevated at that time due to heightened diagnostic efforts at AIDS onset. Although we also had data on malignancies arising 28–60 months after AIDS onset, AIDS-related mortality increases steeply during this late period, and we did not have complete survival data. Therefore, to avoid inadvertently including person-time for subjects with unreported deaths (and thus underestimating incidence), we censored follow-up at 27 months after AIDS onset.

Observed malignancies were categorized by site (and, for lymphomas, leukaeemias, and melanoma skin cancer, by histology) based on the second edition of International Classification of Diseases for Oncology (ICDO-2) (Percy et al, 1990). Under the Working Formulation (Non-Hodgkin’s lymphoma pathologic classification project, 1982), non-Hodgkin lymphomas were classified as low-grade (ICDO-2 codes 9670–9671, 9691–9696); intermediate-grade (9672–9676, 9680–9683, 9697–9698); high-grade, further classified as Burkitt (9687), large cell immunoblastic (9684), or other high-grade (9685–9686); or other/unspecified (all other codes from 9590–9595 and 9670–9714). For calculating post-AIDS incidence of non-Hodgkin lymphomas, we excluded subjects who had non-Hodgkin lymphoma in the AIDS period. Similarly, for cervical cancer, we excluded women diagnosed with cervical cancer in the AIDS period.

### Statistical analysis

For each malignancy, association with KS was assessed by calculating the relative risk, defined as the post-AIDS incidence in subjects with KS divided by the post-AIDS incidence in subjects without KS. We calculated 2-sided 95% confidence intervals for these relative risks using an exact method (Breslow and Day, 1987, pp. 91–95).

For malignancies significantly associated with KS, we used Poisson regression (McCullagh and Nelder, 1989) to adjust the relative risks for gender, age at AIDS (less than 30, 30–39, 40–49, 50+ years), race (white, black, Hispanic, other/unknown), and calendar year (1978–1984, 1985–1988, 1989–1992, 1993–1996). We also controlled for HIV risk group (homosexual male vs. other), because most cases of AIDS-associated KS arise in homosexual males, and this group, compared with other risk groups, may have higher risk for some cancers (e.g. anal cancer) due to factors other than KSHV infection. In an additional analysis, we also adjusted relative risks for CD4 counts at AIDS, which were available for a minority of subjects.

Levels of continuous variables were compared between groups using the 2-sample t-test, and the distributions of categorical variables were compared using the χ² statistic. Matlab (Version 5, Math Works, Natick, MA) and S-Plus (Version 2000, MathSoft, Seattle, WA) were utilized for calculations. A 5% level of statistical significance was used.

We calculated the attributable risk percent (the proportion of cancer cases, among those with KS, attributable to having KS) as (RR–1)/RR, and the population-attributable risk percent (the proportion of cancer cases, in the entire AIDS population, attributable to having KS) as pKS × (RR–1)/(pKS × (RR–1) + 1), where RR was the adjusted relative risk for cancer, given KS, and pKS was the prevalence of KS in the population (Hennekens and Buring, 1987, pp. 87–93). Because KS served to identify persons with KSHV infection, these figures are an estimate of the proportion of cases attributable to KSHV infection.

### RESULTS

#### Study subjects

We studied 189 159 subjects: 26 972 (14%) with KS (occurring at any time during follow-up) and 162 187 (86%) without KS (Table 1). The majority (92%) of subjects with KS were homosexual males, and most were white. In contrast, among subjects without KS, only 47% were homosexual males and 57% were black or Hispanic (Table 1). CD4 counts at AIDS diagnosis were available for 67 896 subjects (36%). Among subjects with known CD4 counts, subjects with KS were slightly more immunocompromised than those without KS (mean CD4 counts at AIDS 91 vs. 115 cells mm⁻³, P = 0.0001). 68% of subjects with KS had CD4 counts below 100 cells mm⁻³ at AIDS, compared with 55% of subjects without KS. Age did not differ between the 2 groups.

#### Relative risks for malignancies

For the post-AIDS period, Table 2 presents relative risks associated with KS, for each of the examined malignancies. Unadjusted relative risks were significantly elevated for several histologic categories of non-Hodgkin lymphoma: intermediate grade lymphomas (relative risk 1.50, 95% confidence interval (CI) 1.26–1.78), high-grade large cell immunoblastic lymphoma (2.44, 95% CI 2.00–2.96), and other/unspecified lymphoma (1.45, 95% CI 1.27–1.66). The increase in large cell immunoblastic lymphoma (IBL) resulted in an elevated relative risk for all types of high-grade lymphoma combined (2.06, 95% CI 1.74–2.45). In analyses adjusted for gender, risk group, age, and calendar year, IBL remained associated with KS (adjusted relative risk 1.58, 95% CI 1.29–1.93), but intermediate-grade lymphoma and other/unspecified lymphoma were no longer significantly associated with KS (relative risks 1.05, 95% CI 0.88–1.26, and 1.02, 95% CI 0.89–1.18, respectively). Relative risks for Hodgkin disease, leukaemias, and multiple myeloma were not elevated (Table 2).

For other malignancies (Table 2), only miscellaneous (‘other/unknown’) tumours were significantly associated with KS (unadjusted relative risk 1.88, 95% CI 1.35–2.59; adjusted relative risk 1.69, 95% CI 1.19–2.39). Among subjects with KS, 34 of these miscellaneous tumours (65%) were classified as ‘malignant neoplasm’ with unknown primary site, compared with 57 (36%) among other subjects (P = 0.0004). Among miscellaneous tumours, tumours were noted at 10 separately specified sites, but none occurred in excess among those with KS (data not shown).
Large cell immunoblastic lymphoma (IBL)

There were 506 IBLs, with 151 occurring in individuals with KS (incidence 0.42%/year) and 355 occurring in individuals without KS (0.17%/year). As noted, the association between KS and IBL was significant even after adjustment for gender, risk group, age, race, and calendar year (adjusted relative risk 1.58, 95%CI 1.29–1.93). In an analysis restricted to subjects with CD4 counts at AIDS, further adjustment for CD4 count did not affect the relative risk (1.50, 1.07–2.10).

The strength of association between KS and IBL did not differ significantly across strata defined by gender and risk group, race, or CD4 count at AIDS (Table 3), or during different calendar periods (data not shown). However, there was some evidence that the strength of association varied across age groups (P = 0.06, Table 3). Among subjects less than 30 years old at AIDS, the relative risk of IBL associated with KS was 1.19 (95%CI 0.63–2.26), which was significantly less than the relative risk among older subjects (2.68, 95%CI 2.19–3.28; P = 0.01 for difference in relative risks). Even after adjustment for gender, risk group, age, race, and calendar year, relative risk of IBL associated with KS was lower for subjects younger than 30 years (P = 0.01).

Primary sites of IBLs among subjects with KS were: lymph node (81 cases, 54%), brain (33 cases, 22%), and other sites (37 cases, 25%). Sites of IBLs among the other subjects were similar: lymph node (192 cases, 54%), brain (64 cases, 18%), and other sites (99 cases, 28%). Notably, among persons with KS, only one IBL (0.7%) was identifiable as a primary effusion lymphoma, with pleura as the primary site. 3 subjects without KS had IBLs arising in the heart. There were no IBLs with peritoneum as primary site.

Immunophenotyping became more common over time, with data available for 0 of 8 IBLs occurring in 1978–1984, 23 of 99 (23%) occurring in 1985–1988, and 155 of 399 (39%) occurring in 1989–1996. For IBLs with immunophenotyping, 168 (94%) were B cell, 9 (5%) were T cell, and one (1%) had neither B nor T cell markers. The occurrence of B cell IBL was significantly associated with a diagnosis of KS (unadjusted relative risk 2.64, 95%CI 1.87–3.69; adjusted relative risk 1.90, 1.35–2.68). T-cell IBL was also associated with KS, although not significantly (unadjusted relative risk 2.87, 0.46–13.44; adjusted relative risk 2.25, 0.52–9.76).

Using the adjusted KS-associated relative risk of 1.58 for IBL, we calculated the proportion of IBL cases attributable to KSHV, assuming that infection with this virus explained the association between KS and IBL, we estimated that KSHV may be aetiologically involved in some AIDS-associated IBLs. As a consequence of our study design, the excess of IBLs that we observed occurred in persons who also had KS. Thus, our results may indicate that specific defects in immune control of KSHV predispose some immunosuppressed individuals to develop either or both of these tumours. On the basis of the magnitude of association between KS and IBL, we estimated that KSHV may be present and etiologically important in 37% of IBLs arising in persons with KS (attributable risk percent 37%). Notably, the estimates of relative risk and attributable risk may have been too low, because some subjects in the referent group (those without KS)
were also KSHV-infected. Nonetheless, it seems likely that the pathogenesis of IBL is complex and multifactorial. Epstein-Barr virus is found in the majority of IBLs and primary effusion lymphomas (Shibata et al, 1993; Nador et al, 1996), and it is possible that this virus acts in concert with KSHV to cause IBL.

Laboratory data, though scant, lend support to our epidemiological findings. In their original description of KSHV in primary effusion lymphoma, Cesàrn and al did not find KSHV in any of 8 other AIDS-associated lymphomas characterized as ‘immunoblastic plasmacytoid’ in histology (Cesarman et al, 1995). Other investigators subsequently found KSHV in 17–22% of IBLs arising outside the pleura (Otsuki et al, 1996; Gessain et al, 1997; Boye Hansen et al, 2000). The level of KSHV in positive cases was low, raising the possibility that the virus was present only in normal circulating B lymphocytes within these tumours. However, in a recent preliminary report, Cesàrn and Knowles described the presence of KSHV in high copy number in tumour cells from 4 additional AIDS lymphomas, all of which were non-effusion IBLs (Cesarman and Knowles, 1999). Although these studies were small, overall they are consistent with KSHV being present and playing a role in a minority of IBL cases arising in AIDS, and are in accord with our estimate of population attributable risk (8%). Other histologic types of lymphoma (e.g. Burkitt or Burkitt-like tumours) have consistently been KSHV-negative in laboratory studies (Cesarman et al, 1995; Otsuki et al, 1996; Gessain et al, 1997).

Additional, conflicting data on the relationship between KSHV and AIDS-associated non-Hodgkin lymphoma are provided by 2 other studies. Using clinical records and autopsy material, Roldolo and colleagues identified 60 cases of non-Hodgkin lymphoma in 363 persons dying with AIDS (Ridolfo et al, 1996). 16 of these lymphomas were found in persons with KS, of which 13 (81%) were ‘large-cell immunoblastic plasmacytoid’ in histology. Notably, individuals whose AIDS index diagnosis was KS were significantly more likely to develop non-Hodgkin lymphoma than those with the more common index diagnosis of *Pneumocystis carinii* pneumonia (relative risk 5.3). On the other hand, Gérard et al observed no difference in KSHV seroprevalence between 63 AIDS lymphoma cases and 126 HIV-infected controls (Gérard et al, 2001). A limitation of the Gérard study, however, was that cases and controls were matched for history of KS, which might have eliminated some differences in KSHV prevalence. Also, serological assays for KSHV can misclassify infection status (Engels et al, 2000).

Lymphomas arising in multicentric Castleman’s disease could partially explain the relationship between KS and IBL. Among HIV-infected persons, KS is associated with the plasmablastic variant of multicentric Castleman’s disease (Soulier et al, 1995; Dupin et al, 2000). In multicentric Castleman’s disease, KSHV is found in plasmablasts in the mantle zone of involved lymph nodes and in secondary plasmablastic lymphomas (Dupin et al, 2000). Plasmablastic lymphomas closely resemble IBL histologically (Dupin et al, 2000; Anagnostopoulos, 2001). Indeed, the ICDO-2 lacks a code for plasmablastic lymphoma, and plasmablastic lymphoma cases might have been classified as IBLs in our study. Nonetheless, multicentric Castleman’s disease is rare (Oksenhendler et al, 1996) and is unlikely to account entirely for our findings.

In our study, the finding of an association between IBL and KS was given strength by its consistency across strata defined by HIV risk group, gender, race and CD4 count. This consistency argues

### Table 2 Relative risks for malignancies in association with Kaposi’s sarcoma

| Site, histology | \( n_{KS} \) | \( n_{KS,KS} \) | Relative risk (exact 95% CI) * |
|----------------|------------|----------------|-----------------------------|
| Non-Hodgkin lymphoma | 632 | 2,260 | 1.60 (1.47–1.75) |
| Low-grade | 5 | 22 | 1.30 (0.39–3.53) |
| Intermediate-grade | 169 | 648 | 1.50 (1.26–1.78) |
| High-grade | 186 | 517 | 2.06 (1.74–2.45) |
| Burkitt | 16 | 70 | 1.31 (0.71–2.28) |
| Immunoblastic | 151 | 355 | 2.44 (2.00–2.96) |
| Other high-grade | 19 | 92 | 1.19 (0.68–1.96) |
| Other/unknown | 272 | 1,073 | 1.45 (1.27–1.66) |
| Leukaemia | 3 | 24 | 0.72 (0.14–2.37) |
| Acute myeloid | 0 | 10 | 0.0 (0–2.01) |
| Acute lymphoblastic | 1 | 1 | 5.76 (0.07–452) |
| Chronic myeloid | 0 | 1 | 0 (0–109) |
| Chronic lymphocytic | 0 | 1 | 0 (0–109) |
| Other/unknown | 2 | 11 | 1.05 (0.11–4.80) |
| Hodgkin disease | 8 | 59 | 0.78 (0.32–1.64) |
| Multiple myeloma | 3 | 10 | 1.73 (0.31–6.71) |
| Oral cavity and pharynx | 7 | 42 | 0.96 (0.36–2.16) |
| Oesophagus | 2 | 8 | 1.44 (0.15–7.21) |
| Stomach | 3 | 16 | 1.08 (0.20–3.77) |
| Small intestine | 0 | 2 | 0 (0–20.0) |
| Colon | 5 | 15 | 1.92 (0.55–5.55) |
| Rectum | 2 | 19 | 0.61 (0.07–2.51) |
| Anus | 5 | 33 | 0.87 (0.27–2.25) |
| Liver | 2 | 19 | 0.61 (0.07–2.51) |
| Pancreas | 0 | 11 | 0 (0–1.80) |
| Upper respiratory sites | 2 | 19 | 0.61 (0.07–2.51) |
| Lung | 22 | 162 | 0.78 (0.48–1.22) |
| Kidney | 0 | 15 | 0 (0–1.27) |
| Bladder | 1 | 7 | 0.82 (0.02–6.40) |
| Breast | 0 | 9 | 0 (0–27.2) |
| Ovary | 0 | 1 | 0 (0–1310) |
| Uterus | 0 | 4 | 0 (0–76.9) |
| Cervix | 2 | 37 | 3.71 (0.43–14.4) |
| Vulva and vagina | 0 | 8 | 0 (0–31.3) |
| Testis | 6 | 16 | 1.79 (0.57–4.82) |
| Prostate | 6 | 22 | 1.30 (0.43–3.32) |
| Penis | 0 | 5 | 0 (0–3.92) |
| Thyroid | 3 | 3 | 5.76 (0.77–43.0) |
| Central nervous system | 7 | 40 | 1.01 (0.38–2.27) |
| Melanoma | 3 | 19 | 0.91 (0.17–3.09) |
| Musculoskeletal sites | 5 | 9 | 3.20 (0.84–10.6) |
| Other/unknown | 52 | 159 | 1.88 (1.35–2.59) |

Abbreviations: \( n_{KS} \) and \( n_{KS,KS} \) number of malignancies occurring in subjects with or without Kaposi’s sarcoma, respectively; CI, confidence interval.

*Relative risks that are in italic are statistically significant (\( P < 0.05 \)). All confidence intervals are two-sided 95% intervals, except when the observed relative risk is zero, in which case the one-sided 95% confidence interval is shown.
against the possibility that unknown factors other than KSHV infection explain the observed association between KS and IBL. Interestingly, this association was strongest in persons at least 30 years old at AIDS onset. KSHV-related risk for IBL may be higher in older individuals due to loss of control of KSHV infection with aging, accumulation of somatic genetic errors, or acquisition of additional cofactors for lymphomagenesis. Alternatively, the association between KS and IBL could have been diluted in younger subjects if clinically inapparent KSHV infection was especially common in that subgroup. Arguing against this second explanation, limited data from cohort studies of homosexual men do not suggest markedly higher KSHV prevalence among younger men (e.g., those born after 1955) (Martin et al, 1998; Melbye et al, 1998).

As noted, the association between KS and IBL was specific. After we adjusted for possible confounders, no other type of lymphoma was related to KS. Risk was increased for miscellaneous tumours, but many of these had non-specific histological codes and may have been misclassified cases of KS. Risk for myeloma was not elevated, which argues against a role for KSHV in this disease despite the controversial identification of KSHV in cultured bone marrow stromal cells from myeloma patients (Berenson and Vescio, 1999; Tarte et al, 1999). Similarly, prostate cancer risk was not increased, even though some epidemiological evidence implicates a sexually transmitted agent (Hayes et al, 2000), and KSHV has been variably found in prostate tissue (Monini et al, 1996; Staskus et al, 1997) and semen (Monini et al, 1996; Howard et al, 1997; Pauk et al, 2000).

Our study complements several previous systematic studies of cancer in KSHV infection. In a survey of South African cancer patients, Sitas et al did not find elevated KSHV-seroprevalence associated with cancers other than KS (Sitas et al, 1999). A potential limitation of that study, however, was its reliance on antibody testing to diagnose KSHV infection (Engels et al, 2000). Using a design similar to that of our study, Biggar et al did not find an excess incidence of malignancies among HIV-uninfected persons with KS (Biggar et al, 1994). On the other hand, among HIV-uninfected Israelis with KS, Iscovich and colleagues noted a 4-fold excess of non-Hodgkin lymphoma and no other elevations in cancer risk except for melanoma (Iscovich et al, 1999). Both investigations provided no data on HIV-infected persons and were hampered by their relatively small size, which precluded detection of increases in rare malignancies.

Despite our study’s large size, we were limited in our ability to identify a potential association for some rare malignancies (e.g., leukaemias). The study was also underpowered to detect associations for female-specific cancers because we had few women with KS. However, there is no other evidence of a casual link between these malignancies and KSHV.

In summary, our study of individuals with AIDS demonstrated an increased risk for IBL among persons with KS. This association with KS was specific among malignancies, remained statistically significant after adjustment for possible confounding factors, and was consistent across subgroups defined by gender, HIV risk group and race. Given the paucity of laboratory data on KSHV in IBL, additional laboratory studies, particularly of IBLs arising in persons with KS, are needed to determine whether KSHV plays an aetiologic role. Further epidemiological studies will also be informative.

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