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Epidemiology of Malignancies in HIV/AIDS

Robert J. Biggar

*National Cancer Institute, National Institutes of Health,
Bethesda, Maryland*

I. INTRODUCTION

Two malignancies, Kaposi's sarcoma (KS) and certain types of non-Hodgkin's lymphomas (NHLs) dominate the cancer types seen in patients with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS). According to the official definition of AIDS (1), the presence of either is considered an AIDS diagnosis in a person known to be HIV-infected, as is KS in a person younger than 70 years old, unless the patient is known not to be HIV-infected. The extraordinary frequencies of either cancer in HIV-infected persons amply justify considering these to be AIDS, but each has a rather different epidemiology and, presumably, etiology. Invasive cervical cancer is also accepted as an AIDS-defining cancer according to official guidelines, although the evidence for an association with AIDS is more tenuous. A variety of other cancers have been reported somewhat more commonly in AIDS patients, including epithelial anal cancers, conjunctival tumors, Hodgkin's disease, and leiomyosarcomas (in children), and these have been suggested to be AIDS-associated. The incidence rates for selected cancers in men (Fig. 1; 2) and women (Fig. 2; 3) at high risk of HIV infection show the influence of the AIDS epidemic on cancer incidence in some populations.

The following description will focus on the cancers most strongly associated with AIDS, providing a brief description of the background, clinical features, and incidence, against which the AIDS-associated cases will be compared.

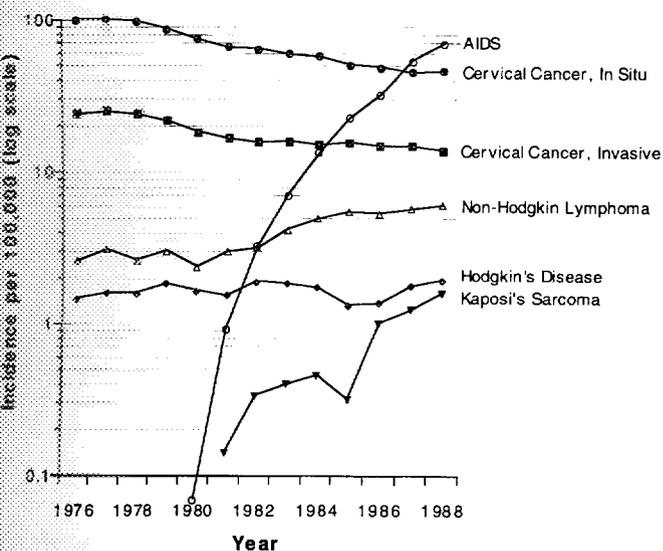


Figure 1 The incidence (log-scale) of selected cancers in never-married men (all races, but preponderantly white) aged 25–54 years old in San Francisco City, over time. Never-married men served as a surrogate for a likely homosexual lifestyle that was available in registry data. However, the authors estimate that only 24% of the observed population was HIV-infected in 1984. Thus, these rates understate the real risk in HIV-infected men. Incidences are presented on a log-scale because of the large increase in KS. Log-scale presentation makes variations in incidences for cancers with less dramatic changes appear minimal; however, a 1-log increase equates to a 10-fold increase and a half-log increase equates to a 3.2-fold increase in incidence. Increases in KS and NHL were most dramatic, but anal cancers and Hodgkin's disease also increased. (Data from Ref. 2.)

KAPOSI'S SARCOMA

A. Endemic (Non-HIV-Related) Kaposi's Sarcoma

1. Clinical Features

Classic KS was first described in 1872 by Moritz Kaposi, a Hungarian dermatologist. He reported that it was an idiopathic, multicentric, pigmented tumor more common in Jewish and eastern Mediterranean men. Over the next century, various "subtypes" of KS were described, first when this disease was found in Africa, then in younger, iatrogenically immunosuppressed transplant patients, and finally in persons with AIDS. KS is often still categorized according to these different subtypes, including "classic Mediterranean," "endemic Africa," "transplant-

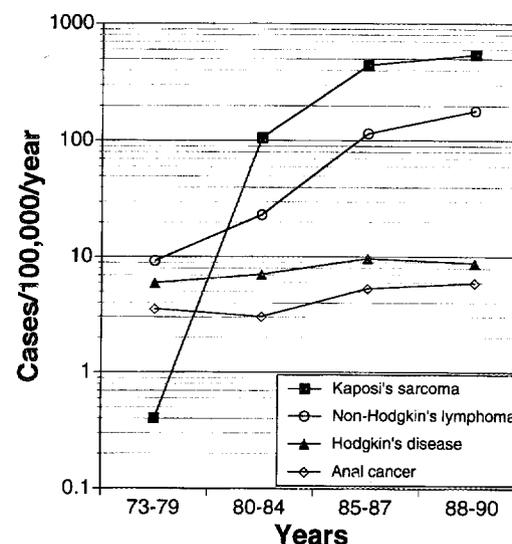


Figure 2 The incidence (log-scale) of selected cancer in black women (regardless of marital status) aged 20–49 years old in New York City, over time. The proportion estimated to be HIV-infected was not provided. However, the increase in AIDS cases in this group attests to their high risk of HIV infection. Although KS and NHL incidences increased, there was a decrease in both invasive and in situ cervical cancer and little change in the incidence of Hodgkin's disease. (Data from Ref. 3.)

related," and AIDS-related." These historical distinctions probably serve little purpose because there are only minor differences between these types. The classic form is typically seen in the elderly and usually has early "plaque" lesions on the limbs at presentation. In some parts of Africa, KS occurs at much higher incidence than in the United States; hence, patients present at younger ages and, because of poorer health care access, usually have the more advanced nodular disease. Neither the classic nor African types have documented immunological abnormalities; therefore, they are sometimes called "endemic KS" to distinguish them from immunosuppression-related KS. However, the emerging understanding of the common role of human herpes virus type 8 (HHV-8; KSHV) in all forms of KS suggests that they are the same condition in all settings.

The malignant cells are considered to be spindle cells, most likely of endothelial origins, although this is somewhat uncertain (4,5). Until recently, KS was often suggested to be a polyclonal response of vascular endothelial cells to an unknown stimulus. However, at least in nodular lesions (which could represent

the more-advanced form of this disease), the cells have now been shown to be clonal in origin (6), with lesions at different sites all derived from the same clone, which suggests metastasis (7).

In nonimmunocompromised persons (endemic KS), KS generally first appears on the extremities, particularly the lower legs and feet (8,9). Initially, there may be flat, purplish lesions (plaques) that subsequently become more nodular and invasive of tissues around them. The purplish hue of the lesions is due to the rich vascularization of the KS tissue and extravasation of erythrocytes. Regional nodes may become involved. However, even in the absence of lymphadenopathy, lymphedema of the involved limbs may be pronounced. In patients with endemic disease, the disease is typically indolent or slowly progressive over years, although when it occurs in young persons, it may be more aggressive. It has been found in almost all organs except the brain, but internal tumors rarely cause serious clinical problems in nonimmunocompromised persons. Medical management is relatively easy when adequate facilities are available, and death of other causes is more likely than that of the tumor itself. In areas without adequate medical care, such as parts of Africa, secondary infections and disability are major contributors to mortality, even when the cancer is considered to be the primary cause of death.

2. Incidence

Before the AIDS epidemic, KS was already recognized to have peculiar epidemiological features. In the United States, it was a rare tumor, threefold more common in men (0.29:100,000, age standardized) than women (0.09:100,000) (10). Incidence rates in blacks are about half those of whites, but some of this difference may have been because of diagnostic bias. Figure 3 illustrates the geographic distribution of areas with higher incidences of endemic KS. In western Europe, rates were similar to American rates but were lower in England and Denmark and slightly higher in Sweden and Italy (11). In Mediterranean and eastern European areas, rates were threefold higher, about 1:100,000 persons, with persons of Jewish and perhaps also Arabic origin being at highest risk.

Even higher rates of KS occurred in parts of Africa (see Fig. 3), although quantifying the precise incidence is difficult because of lack of reliable data. Given the HIV epidemic in Africa and its effect on KS, it is now especially hard to determine the rates of non-AIDS-related KS in this region. The highest incidence for endemic KS has been reported for areas of East Africa, from Uganda to Zambia. In eastern Zaire, 8% of all tumors were reported to be KS in 1960 (12,13), long before the AIDS epidemic affected this area. In Africa, KS has been reported to occur up to tenfold more commonly in men than women, but some of the differences in gender found there may have been due to referral bias, because women may be less likely than men to obtain medical attention.

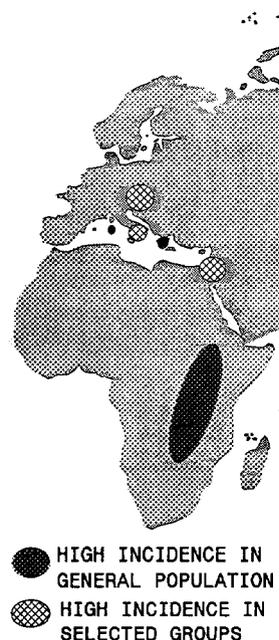


Figure 3 The distribution of high-incidence areas of endemic Kaposi's sarcoma. The highest incidence areas are in East Africa. Relatively high rates are found in older members of general populations of Greece, Sardinia, and perhaps parts of southern Italy. In Eastern Europe and Israel, rates are high in the Jewish populations. Rates in Asian populations are very low (even among persons with AIDS). Immigrants from these areas have rates similar to the original populations.

In all areas, endemic KS incidence increases markedly with age. In low-incidence areas, it is rarely diagnosed in immunocompetent persons younger than 70 years old. However, in Africa, where the incidence of endemic KS is high, cases regularly occur in adolescents and even in children (14,15). However, adults and children with non-AIDS-related KS in Africa appear to be immunocompetent, at least with available measurement of immunity (16). The clinical manifestations appear to be more aggressive in younger persons, and lymph nodes and internal organ involvement may be prominent (14,15). In the United States and Europe, endemic cases in childhood are very rare.

The high incidence of KS in younger persons with iatrogenic immunodeficiency related to transplantation is discussed in Chapter 2.

B. AIDS-Related Kaposi's Sarcoma

1. Clinical Features

Although KS in persons with and without AIDS has a similar appearance under the microscope, the clinical presentation of KS in AIDS patients is typically more abrupt and widespread than it is in non-AIDS-related KS. Lesions are usually purplish macules or only slightly raised papules. In contrast with endemic KS, multiple lesions often appear in AIDS-related KS and these are most often on the trunk or the head and neck. They may also appear in mucous membranes, sometimes as the only recognized site. These are most noticeable in the mouth, but internal lesions can be found throughout the gastrointestinal tract or in other organs (17,18). The KS lesions are rarely life-threatening, although involvement of internal organs, such as the lung, can be. The lesions on the skin are frequently cosmetically disturbing and may cause disability, requiring therapy for control. Median survival of patients with AIDS-related KS was 14–18 months in the early 1990s (19,20), which was relatively long for an AIDS-defining illness; it is likely to improve with advances in therapy. As with non-AIDS-related KS, patients usually die of another condition related to their immunosuppression.

2. Incidence

The incidence of KS in patients with AIDS varies considerably by HIV-exposure group (Fig. 4). Among homosexual and bisexual men, the risk is five- to tenfold higher than it is in other AIDS groups, even after adjusting for age, race, and calendar-time (21). Interestingly, incidence does not increase with age, as it usually does with cancers, even in the AIDS setting. Rather, in homosexual men,



Figure 4 Declining risk of AIDS-related KS risk, over time: Data were adjusted for age and race differences in incidence. These declines were seen in both homosexual and nonhomosexual male AIDS cases. (From Ref. 21.)

KS peaks in 30–39 year olds, whereas in nonhomosexual men, younger adults have the highest incidence (Fig. 5). The relative incidence of KS has been well defined in cohorts of patients who present with another AIDS illness. During the period 6 months to 1 year after AIDS onset, the excess of KS is over 100,000-fold in homosexual men and 13,000-fold in nonhomosexual men, compared with age-, sex-, and race-matched rates in the general population during the pre-AIDS era (21). Never-married men in San Francisco, a surrogate for homosexual men, do not appear to have had an increased risk of KS before the AIDS era (22). Among nonhomosexual men or women with AIDS, only 2–3% of cases manifest KS as the first evidence of AIDS. Within HIV-exposure groups composed of both sexes (e.g., intravenous drug users and transfusion recipients), the relative risk of developing KS is lower in women than men (Fig. 6; 23).

The proportional and absolute risk of KS has also varied over time (24–26). Among the earliest cases of AIDS in homosexual men, 40% had KS as their first manifestation of AIDS, whereas, in the most recent years, it has been about 12%. This same variation by risk group is seen in KS incidence following another AIDS diagnosis, which is also falling in both homosexual and nonhomosexual men (see Fig. 5; 21). Intravenous drug-using men have a somewhat higher frequency of presenting with KS than other nonhomosexual men, but some of these could be men who have had sex with men in exchange for drugs, but who do not identify themselves as homosexual or bisexual. There may be several reasons for this decline. Minor lesions are now appreciated as non-life-threatening by both doctors and patients, and KS may be less completely reported to cancer registries. In addition, as the lifestyle of at-risk homosexual and nonhomosexual persons has changed to avoid HIV in the post-AIDS era, this may have also lowered exposure to other causal factors.

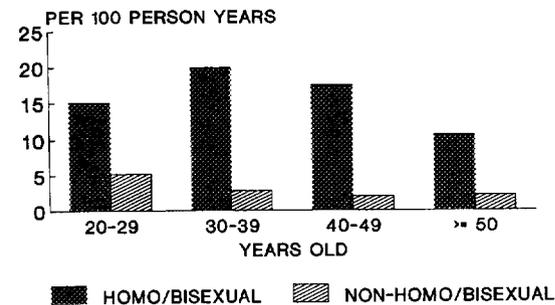


Figure 5 Percentage of AIDS cases who have ever had KS; by age: Data adjusted for differences in incidence by race. The peak incidence in homosexual men is 30–39 years old, whereas nonhomosexual men peak in their 20s and decline thereafter. (From Ref. 21.)

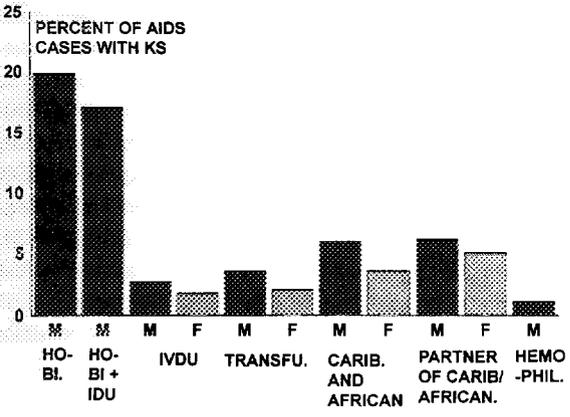


Figure 6 Percentage of men and women in different exposure categories who present with KS as the AIDS-defining illness: The higher risk in men with homosexual lifestyles is obvious. In addition, for exposure categories with both genders, males consistently have a higher risk than females. (From Ref. 23).

In patients with HIV infection, KS may appear at almost any stage of immunosuppression, but it is rare when immunity is near normal. Because KS can occur earlier than other AIDS-related illnesses in the course of HIV-related immune deterioration, the average CD4 counts are higher than are seen in many other AIDS illnesses. However, as immunity deteriorates, KS also becomes more frequent (20,27). Viewed as time from AIDS, the risk of KS nearly doubles in 12 months (21). During this period, immunity probably declined. As antiretroviral therapies become more effective, immunological improvements could lead to disappearance of KS lesions, given that spontaneous remissions of KS occur when immunosuppressive therapies are stopped in organ transplant recipients with KS. Thus far, this has been observed only occasionally in AIDS patients.

Cases of KS have been reported in homosexual men who are not HIV-infected and who are immunologically normal (28–30), but whether the number of cases exceeds those expected is unclear. Because of intensive medical surveillance of this population, there may be diagnostic bias in which early small KS lesions have been more commonly detected. However, these cases may also indicate the presence of causal factors, in addition to HIV, to which homosexual men may be exposed by their lifestyle.

3. Etiology

Over the past two decades, epidemiological studies have associated KS with various factors. These studies have been mostly conducted among homosexual men

because of the high incidence of KS in this group. The findings have been difficult to interpret because they usually involve multiple associations that are, in turn, related to each other.

The common thread is that the most sexually active and “adventurous” subjects are at greater risk of KS, whether this is measured as a greater number of sexual partners (31), more oral–anal contact (32–34), more frequent infections with sexually transmitted infections (35,36), more drug use (especially of nitrite inhalants; 37,38), or sexual partners from communities of high HIV incidence (24,39). Despite attempts to disentangle the confounding by lifestyle, it has been difficult to discern which, if any, are the critically important factors or whether none of them really bears on the cause of KS. More impressive is evidence that women who were HIV-infected by bisexual partners were more likely to have KS as an AIDS illness than those infected by heterosexual partners (Fig. 7; 23,40,41).

The associations with sexual behavior were weak, and most findings were confounded by earlier exposure to HIV among persons with high-exposure–risk lifestyles. Thus, persons infected earlier will progress to immunosuppression sooner and manifest KS earlier. Furthermore, various sexually transmitted infections are spread by similar routes within these groups and thus could be considered as possible etiologic cofactors of KS by such studies. Many such candidate

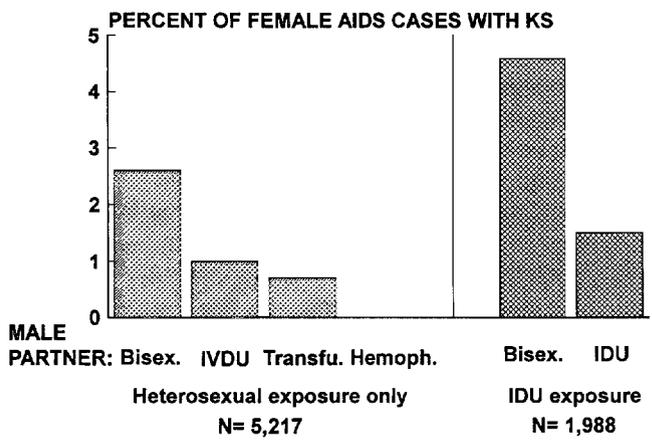


Figure 7 The difference in KS risk for women with AIDS, by exposure category of their sexual partners: Women were further separated into those without (heterosexual exposure only) and with exposure to intravenous drugs. For women in both categories, the KS risk was higher when they had bisexual partners, implying sexual transmission of a causal agent that is more common in bisexual men. (Data from Ref. 23.)

cofactors have been proposed: cytomegalovirus (42), *Rochalimaea henselae* (43), human papillomaviruses (HPV; 44), and *Mycoplasma fermentans* (45). However, only the recently described human herpesvirus-8 (HHV-8; see following section) meets the necessary criteria to be considered causal.

Although there may be an infectious etiology for KS, other noninfectious conditions could influence the development of the disease. Genetic susceptibility has been proposed. Initial studies suggested a higher risk in homosexual men with HLA-DR5 than in men with other HLA types (46,47). However, DR5 associations have not been confirmed in later studies of either non-AIDS-related or AIDS-related KS (48-50). Other HLA correlations have been reported, but none is consistently found in all studies (51).

Consistently higher rates of KS are found in men than in women, both with and without AIDS, when men and women of the same exposure groups are compared (see Fig. 4). This could indicate that hormonal factors are important. In vitro, hormones (human chorionic gonadotropin, or a closely related substance) appeared to accelerate apoptosis of KS cells (52). A recent study reported higher testosterone levels in homosexual men with KS than in those with other AIDS-defining illnesses, after adjusting for CD4 cell counts (53). In another study, however, lower testosterone levels were observed in KS cases, although the difference was not statistically significant (54).

Relation to HHV-8. In late 1994, investigators reported finding a new human herpesvirus (the eighth known human herpesvirus; hence, HHV-8) in KS tissues derived from AIDS patients (55). It was soon determined that this virus is also present in nearly all forms of KS, regardless of their geographic location, the age of the subject (56,57), or the degree of immunosuppression. Therefore, HHV-8 is often referred to as the "Kaposi's sarcoma herpesvirus (KSHV)." This strong association between KS and HHV-8 provides compelling evidence that KS in all areas and conditions are forms of the same disease process and that this virus is etiologically important to, and perhaps the cause of, both endemic and immunosuppression-related KS.

Human herpesvirus-8 is a member of the gamma herpesvirus group, along with Epstein-Barr virus (EBV) and the primate virus, herpesvirus saimirii. Both EBV and herpesvirus saimirii have been associated with NHL and, notably, HHV-8 is also strongly associated with a specific form of NHL called body-cavity-based lymphoma (BCBL) or primary effusion lymphoma (58).

The epidemiology of this new virus has yet to be well established. The primary difficulty relates to methods of detection, which have been molecular, largely based on polymerase chain reaction (PCR) tests performed on tissue. On average, BCBLs have 40-80 HHV-8 copies per cell, whereas KS cells have about a single copy per cell (58). HHV-8 can be detected in circulating peripheral B

lymphocytes in only about 50% of persons with AIDS-related HHV-8-positive KS; in those with detectable virus, the number of copies per cell is on the order of 1:1000 cells.

A validated antibody test capable of detecting evidence of prior infection will be needed to determine the epidemiology and natural history of HHV-8 infection. First-generation assays, some using latent and others using lytic antigen, have provided diverse results. Overall, in high-risk subjects, such as homosexual men without KS, the prevalence varies from 20 to 40%, whereas in normal blood donors, the prevalence is between 2 and 20% (59,60). However, these assays often disagree about which individuals are seropositive in the normal population (personal data), limiting conclusions about the distribution of this virus in the general population.

Furthermore, the tests appear to be insensitive. Only about 70-80% of AIDS patients with KS cases have detectable antibodies (60,61). Almost all KS cases have HHV-8 detected by polymerase chain reaction and probably all are infected. Thus, antibody levels to this virus appear to be near the sensitivity of existing tests, perhaps because the level of the virus (and, hence, antibody levels) are low. Consequently, in population studies, it is still unclear whether some assays are giving nonspecific results, or others are specific, but insensitive, for detecting infection. Given the pace of development and the emerging ability to grow the HHV-8-infected cells in culture, there should be rapid improvements in these assays.

Despite the current inadequacy of serological tests, data about the routes of HHV-8 transmission are emerging. Analyses of subjects without disease consistently show that homosexual men have a higher prevalence of antibodies to HHV-8 than other groups (60,61), implying that some aspect of their lifestyle leads to an increased risk of exposure. Antibody prevalence is higher in men with more sexual partners, suggesting that sexual transmission is important. Both anal intercourse and oral-anal contact have been proposed as routes of transmission.

Finally, cohort studies appear to indicate that the risk of HHV-8 infection increased in the early 1980s and fell thereafter (62). This is consistent with the notion that HHV-8 became more widespread during the era when HIV and other sexually transmitted agents were also being spread epidemically, probably as a consequence of greater numbers of sexual partners among homosexual men in those years. The decline in recent years is also consistent with the decline in KS seen recently, presuming that the incubation period between infection and illness is short, as studies using polymerase chain reaction for detecting HHV-8 appear to indicate (59). However, all of these data must be viewed with caution for the sensitivity and specificity of the assays remain to be established.

III. NON-HODGKIN'S LYMPHOMA

Non-Hodgkin's lymphoma (NHL) is relatively common in young American adults in the age range for AIDS, having an incidence of 8 cases per 100,000 in males 20-54 in 1982 (statistics from Ref. 63 unless other specified). Thus, the increased incidence of NHL in AIDS patients was not as quickly appreciated as was the high incidence of KS. However, by 1982, it was appreciated that AIDS patients had a high risk of unusual, high-grade NHLs, including immunoblastic and Burkitt-like lymphomas (63a), an excess that was soon confirmed by registry surveillance studies (63b). Despite a high absolute risk of NHL in AIDS patients, the relative risk has been far lower than for KS because of the relatively high background rates of NHL.

The clinical and pathological profiles of NHL vary somewhat by the source of the data. Case series emphasize the more unusual manifestations of the tumors; therefore, reports may overstate their frequency because of investigator bias. However, registry-based data may contain only the initial or predominant NHL site or the site from which a biopsy was taken and thus be incomplete. For example, early in the AIDS epidemic, extranodal involvement was reported in 80% of patients with AIDS-related NHLs (63a). In contrast, registry data record 40% of AIDS-related NHLs as having extranodal involvement (63). This proportion is higher than is reported for non-AIDS NHLs (25%), which confirms the clinical impression that extranodal involvement is more frequent in AIDS patients, but it may understate the real frequency of this condition. Thus, sources of data should be noted when composing a clinical profile. The following discussion compares non-AIDS- and AIDS-related NHL using registry-based data.

A. Non-AIDS-Related NHL

1. Clinical Features

Non-Hodgkin's lymphomas account for about 4% of all cancers in the United States. About 85% are B cell in origin and the remainder are T cell or null cell. Almost all tumors are clonal, exhibiting uniform immunoglobulin heavy- and light-chain gene rearrangements, but biclonal or polyclonal tumors also have been reported (64,65). They include a large number of histological types that have different clinical courses. Different classifications have been used to categorize these tumors into related groups. However, these tumors may be pleomorphic and complex, making morphological classification difficult. For clinical convenience, NHL histologies that have progressively worse prognoses are grouped together by the Working Formulation by grade (66). This system is often used in studies of AIDS-related lymphomas. The grade categories include low (25%), intermediate (45%), or high (12%) grade, but some are not classified (18%) or grade is not

specified (10%). The prognosis of NHL is relatively good. Nearly half (45%) of all patients surviving for 5 years. However, the median survival in patients with the high-grade (worst prognosis) NHL is about 18 months.

The most common presenting feature of NHL is lymph node enlargement, but extranodal lymphomas are frequent (20-30%) at presentation and may be found in a variety of sites (67). Nodal and extranodal tumors have a similar distribution by grade. About 2% of NHLs (10% of extranodal NHLs) in non-HIV-infected persons are primary lymphomas of the brain (68). The incidence of primary brain lymphoma is increasing in non-HIV-infected persons (69,70). Some but not all of this increase may be due to better ascertainment because diagnostic methods have improved in more recent years. When classified, most brain lymphomas have high (20%) or intermediate (50%) grade histologies in HIV-uninfected patients.

2. Incidence

In 1992, the overall age-standardized incidence of NHL in the United States was 15:100,000. In large part because of AIDS, incidence in young (20-54 years old) persons almost doubled (to 14:100,000) between 1982 and 1992. However, for several decades NHL incidence in the general population of non-HIV-infected persons has also increased, at a rate of about 4% per year (67,71). The reasons are unknown. This increase includes many subtypes of lymphoma, but high-grade NHLs are increasing most rapidly (72). NHL incidence increases exponentially with age, but the incidences of specific subtypes have different patterns and differ markedly by geographic areas. For example, Burkitt's lymphoma, a high-grade NHL, is the most common childhood tumor in tropical Africa and New Guinea, but rare elsewhere. Overall, the lymphomas as a group are about 1.5- to 2-fold more common in the persons of upper economic and educational status, in the white population and in men (26).

In both genetic and iatrogenic immunodeficiency conditions, about half of the cancers seen are NHL, with 22% of these involving the central nervous system (CNS; 73-75). Many of the lymphomas have high-grade histological classifications, usually of the immunoblastic type. In contrast with AIDS cases, they do not have a high risk of Burkitt's or Burkitt-like lymphomas (76). In organ transplant recipients, NHL incidence rises more slowly than the excess of KS, but faster than other transplantation-associated tumors (77). In bone marrow transplants, NHLs are also the most common cancer (78). Incidence is higher when HLA types were imperfectly matched (79), suggesting that chronic antigenic stimulation might be important.

3. Etiology

Whether all types of lymphoma are part of the same spectrum of disease (e.g., tumors arising at different points in the maturation of the cell type) or should be

considered as tumors with different etiologies is unclear. In some settings, including AIDS, the incidence of several different types of NHL are increased, suggesting they are part of the same disease spectrum and could have a similar pathogenesis. However, other types have distinct epidemiological patterns; therefore, they presumably have different etiologies. Certainly, the specificity of some genetic and environmental associations, such as the 8:14 translocation in Burkitt's lymphoma and its association with EBV, argue that the molecular pathways promoting the growth of different NHL types are diverse.

Epidemiologically, non-AIDS-related NHLs have been associated with various environmental factors, such as farming occupations, herbicide exposure, and prolonged antigenic stimulation. In addition, infection with EBV, a B-cell tropic virus, appears to be important in some tumors, perhaps by enhancing the development of immortalized B cells that are susceptible to malignant transformation.

B. AIDS-Related NHL

1. Clinical Features

Clinicians caring for AIDS patients quickly appreciated that NHLs were occurring in excess. The lymphomas seen were most commonly high (40%) or intermediate grade (32%) or unclassified (27%), with only 2% being low grade. Among high-grade tumors, immunoblastic and Burkitt-like lymphoma predominate, whereas among the intermediate-grade tumors, most have diffuse, large-cell histologies. Extranodal distribution is more common (40%) in AIDS-related NHL, but the site distribution is generally similar to non-AIDS-related cases (80), with the exception of a marked excess of primary lymphomas of the brain, which represented 20% of all NHL cases in AIDS patients. Most primary brain lymphomas have high (40%) or intermediate (55%) grade histologies (68,70).

The grade classification of NHL was developed to clarify the relation between histology and prognosis. However, AIDS patients with lymphoma do poorly (median survival: 6 months) regardless of the grade of their NHLs (80). The median survival of primary lymphoma of the brain was even worse (median survival: 2 months; 68,70). The poor prognosis probably reflects the underlying immunosuppression of the patients with AIDS-related NHL. When NHLs occur in persons who are not severely immunocompromised, they may respond well to therapy; however, many tumors occur at a time when immunity is severely immunocompromised. These patients tolerate chemotherapy poorly and often die of other immunosuppression-related illnesses.

2. Incidence

Overall, about 3% of AIDS patients present with NHL (26). As with NHL in persons without AIDS, risk increases with age (Fig. 8). In AIDS patients who

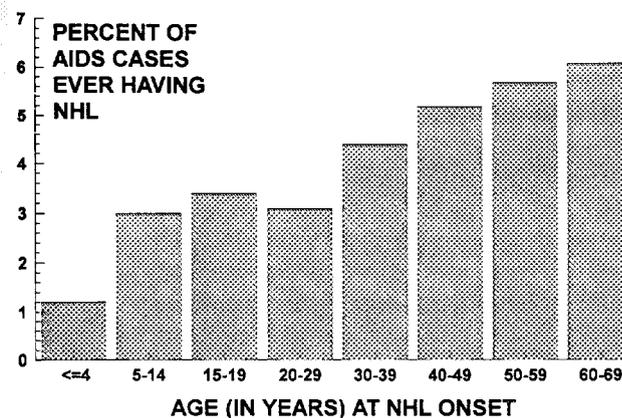


Figure 8 The risk of NHL in AIDS cases, by age (unpublished data from AIDS-cancer registry linkage studies): The rising risk is similar to that seen in persons without AIDS.

present with other conditions, the relative risk of developing NHL is 200- to 300-fold higher than in age-, sex-, and race-matched background population. NHL risk by exposure group varies modestly by group, being higher for men than women, and higher for whites than blacks (Fig. 9). These same demographic features are known to affect NHL risk in non-AIDS NHL. Although there is also some variation in NHL risk by HIV exposure category (see Fig. 9), these become minimal after adjusting for the demographic differences between the groups. Children have a lower risk of presenting with lymphoma, and among children and adolescents, Burkitt-like lymphomas are more frequent (26,76).

According to AIDS registry data, about two-thirds of all NHLs are diagnosed at the time of AIDS onset, and the remainder are diagnosed after another AIDS illness. However, about as many cases occur after AIDS as at the time of AIDS onset, but half of these later cases are never reported to AIDS registries (21,80). On death certificates, 5.7% of AIDS cases have NHL listed among their causes of death (81). The absolute risk of brain lymphomas is about 0.5-1%, which is 3600-fold higher than the risk in the general population (70). These tumors tend to have immunoblastic-plasmacytoid histological presentations (82).

By type, the highest relative risk is for high-grade NHL. Overall, the relative risk of NHL is about 200-fold above that of the general age-, sex-, and race-matched population: 377-fold for high-grade, 111-fold for intermediate-grade, and 17-fold for low-grade lymphomas. Even a small degree of misclassification could account for the small excess of low-grade tumors. By specific histological characteristics, the highest relative risks are for immunoblastic (650-fold), Burkitt-like lymphomas (250-fold), and large-cell, diffuse (145-fold) (80). AIDS-

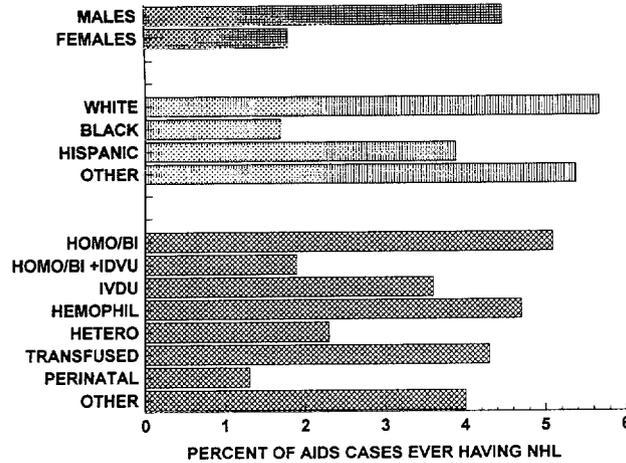


Figure 9 The risk of NHL in AIDS cases, by gender, by race, and by HIV exposure category (unpublished data from AIDS-cancer registry linkage studies): The higher risks in males and whites are similar to the pattern found for NHL risk in persons without AIDS. The majority of homosexual men and persons with hemophilia or transfusion exposure are white, whereas the majority of intravenous drug users are black, accounting for the differences seen between these groups.

related NHL tend to be more pleomorphic than non-AIDS NHLs (83) and may have plasmacytoid features (84). It is unclear if extranodal plasmacytomas are increased among the AIDS-related lymphomas (17). Miscellaneous (2%) or non-specific (25%) histological types are more commonly reported to registries, which could reflect difficulty in classification.

The added public health burden of AIDS-related NHL depends on the frequency of AIDS in the population. In 1990 in San Francisco, an epicenter of the AIDS epidemic, AIDS-related NHL accounted for about 60% of the NHL being diagnosed, whereas in Atlanta and New Jersey, about 24% of the NHL was AIDS-related (80). In areas where AIDS is less prevalent, the public health burden of the AIDS-related lymphomas is lower (80).

3. Etiology

The etiology of AIDS-related NHL is largely unknown. The NHL cells are almost all of B-cell lineage and not themselves HIV-infected. Chronic antigen stimulation may contribute, but cannot be causal alone, for excesses of NHL do not occur until immunity wanes, but HIV viral particles, which are highly immunogenic, are constantly produced throughout the course of infection (85,

86). Although associated with depressed immunity, it is unclear whether the etiology of NHL is related to immunosuppression itself, or to the immune dysregulation associated with the immunosuppression. In persons with AIDS, there is both immunosuppression of CD4+ T cells and intense immunostimulation of B cells (87).

Given that these tumors exhibit a range of chromosomal abnormalities and translocations similar to that in NHL among non-AIDS-related persons, these anomalies seem likely to be a common part of the pathway toward malignancy. Perhaps the rapid turnover of the cells increases the frequency of genetic errors. They may be driven by attempts to compensate for immunosuppression, by intense stimulation from antigenic exposure to circulating viruses, or by cytokines released from virally infected cells. However, in non-AIDS organ transplant recipients, NHLs may remit when iatrogenic immunotherapies are withdrawn, which argues that control of the malignant cells is possible, even if the malignancy is already a clonal outgrowth.

Epidemiological studies have not yielded dependable leads to the etiology of NHL. The demographic characteristics of the AIDS-related cases (older age, male, white, and higher socioeconomic status; 26) resemble those seen in non-AIDS-related cases. Geographically, there is little variation in incidence (88). NHL incidence in AIDS may be lower in Africa than elsewhere (89-92), but the data are weak. Unlike KS, the risk of NHL is generally similar in different risk groups. In the United States, the risk is somewhat higher in homosexual men, but this difference may be partly attributable to the demographic features of homosexual men, who tend to be affluent, urban, and white (26). In European AIDS cases, intravenous drug users have a slightly higher rate of NHL than homosexual men (93). No occupational exposures are known to influence NHL risk in AIDS. Hair dyes have been implicated as possibly etiologic factors, in other studies of NHL, but hair dressers who died of AIDS had no greater risk of NHL than other persons with AIDS (94). There is no indication that antiretroviral therapies increase the risk of NHL, a theoretical concern (95,96).

Of infectious agents, the virus most commonly associated with lymphomas is EBV. Almost all brain lymphomas have a clonal episomal EBV infection (97,98), as do many (50-70%) immunoblastic lymphomas and other NHLs (30-40%; 99,100). The association with EBV is thus stronger for the AIDS-related than non-AIDS-lymphomas, in which about 20% have clonal EBV infection. Furthermore, HIV-infected, immunocompromised persons have high numbers of circulating EBV-infected B cells (101) preceding the developing of lymphoma (102). Possibly the route to malignancy includes expansion of the EBV-infected B-cell clones that are then susceptible to another transforming genetic event (103).

One B-cell malignancy, primary effusion lymphoma (PEL), has special interest for its association with another herpesvirus, HHV-8. This is a rare malignancy

nancy even in the setting of AIDS. On the basis of some unusual clinical features and surface markers, it was first described as a specific type of tumor in 1989 (104). With the discovery of HHV-8 and its relations to KS, many NHL types were screened. Although this virus is not associated with other NHLs, it is strongly associated with PEL (58). Almost all PELs have this virus in high-copy number. Although there is no evidence that NHL incidence is higher in persons with KS, who are also HHV-8-infected, there are too few PEL cases to determine if this specific NHL is higher in KS patients. Most of the PELs are also EBV-positive (58).

A rare form of polyclonal tumors, called multicentric Castleman's disease, is closely associated with KS in AIDS patients and also harbors HHV-8 (105).

The T-cell malignancies in AIDS are rare (106). However, because T cells are susceptible to HIV infection, it has been possible to examine if HIV is clonally integrated. In a few instances, HIV integration has been reported to be adjacent to one of the proto-oncogenes (*c-fps/fes*) in the tumor cell genome (107,108). This could be a rare example of HIV acting through insertional mutagenesis.

IV. OTHER CANCERS

Many other tumors have been reported in persons with HIV-AIDS. Given the large number of persons with HIV and AIDS, now more than a million living and dead in the United States alone, it is no surprise that virtually any tumor can, by chance, appear in such a person. At issue is which tumors, other than the very obvious KS and NHL, are increased in frequency. Both cohort and registry-based approaches have been used to examine this question. However, few cohorts have enough HIV-infected persons to provide robust estimates of these rare events, whereas registry data do not generally include data about HIV-infection or risk factor data about groups possibly exposed to HIV. Study size concerns limit firm conclusions about which tumors occur in excess, but results in different studies have yielded generally similar findings.

Recently, it has been possible to link AIDS and cancer registry data directly, preserving confidentiality by erasing personal identifiers before data are taken for analysis. This provides a very large number of subjects known to be HIV-infected (because they had AIDS). Even these studies are not easily interpreted because of possible biases. Specific subgroups may have excess exposures to other potentially carcinogenic agents, such as greater levels of smoking and more exposure to hepatitis B and C in drug users and hemophilic persons. Because of health sensitivity and concern about sexually transmitted diseases, homosexual men may receive better than average medical care, for example, but drug-using persons and minorities may receive less than average care. Furthermore, doctors caring for HIV-infected persons or persons with AIDS may intensively screen

patients at the time of AIDS, detecting cancers and other diseases at an unusual frequency. However, they may be less aggressive about pursuing possible signs of malignancy in late-stage HIV illness. Finally, many tumors are found only at the time of autopsy, but the autopsy rate in patients dying of AIDS may differ from those dying of other causes. Thus, both absolute and relative rates of difference between HIV-exposure groups and normal populations must be considered as estimates.

In one linkage study, the relative risk of all cancers other than NHL was marginally increased (1.5-fold, 95% confidence interval, 0.95–2.3) in a series of nearly 5000 persons followed after developing KS-related to AIDS (109). Specific types may occur in excess, as discussed later, but there has been no general increase in all cancers. However, tumors in profoundly immunosuppressed persons can be difficult to manage and will have a poor prognosis, reflecting the underlying conditions. This management dilemma does not indicate any difference in the fundamental tumor etiology or biology. In HIV-infected persons who are not severely immunocompromised, therapy may be very successful.

A. Cervical and Anal Cancers

During the late 1980s, women with AIDS were reported to have a high frequency of in situ cervical carcinoma, and unusually aggressive cases of invasive cervical cancer were noted (110,111). Among treated women, tumor recurrence was more common in the HIV-infected group (112). Several studies supported these findings by showing a higher frequency of cervical dysplasias, indicative of human papillomavirus (HPV) in HIV-infected women (113,114). In HIV-infected women, HPV infection was generally persistent, rather than self-limited, especially in immunosuppressed women (115,116), and carcinoma in situ was more common in women with immunosuppression (112,117). From this evidence, the Centers for Disease Control and Prevention (CDC) classified invasive cervical cancer in an HIV-infected woman as an AIDS-defining malignancy in 1993.

However, not all evidence supports considering cervical cancer to be AIDS related. Most studies have not adequately accounted for bias. Women with HIV infection are usually exposed by heterosexual activity or drug use. Often these women have many sexual partners or their sexual partners have many partners. Therefore, as a group, these women have a high frequency of sexually transmitted viruses, including HPV types associated with cervical dysplasia and cancer. When women with similar sexual exposures are compared, such as prostitutes in Africa, it is not clear if the HIV-infected group is more likely to be HPV-infected or to have abnormal cytological results (111,118). In registry-based studies, the incidence rates of invasive or in situ cervical cancers have not increased among women living in New York City (3), which is in contrast with the rates of AIDS and other AIDS-related malignancies in women (see Fig. 2). Similarly,

in parts of Africa with rampant heterosexual HIV transmission and many women infected, cervical cancers have not increased (119,120). Furthermore, there is a quality of care bias. At one clinic, among women with abnormal cervical smears, those who were HIV-positive were significantly less likely to receive adequate follow-up because they returned for results less commonly (121). Thus, the advanced stages of cervical cancer seen in such women may reflect social problems, rather than biology.

In registry linkage studies, the incidence of cervical dysplasia in women with AIDS was elevated about fourfold, but in this group it was also elevated about fourfold for up to 5 years preceding AIDS (Fig. 10; 122), a time when they were probably relatively immunocompetent. Furthermore, although aggressive cases of invasive cervical cancer have been reported in women with AIDS, there does not appear to be a distribution of cases that is weighted toward unusual severity. These data suggest that cervical cancer is not epidemic, but it is possible that, at least in the United States, screening for early indications of HPV infection and aggressive early therapy of in situ disease might have blunted the appearance of invasive carcinoma. It is difficult to apply this explanation to African women,

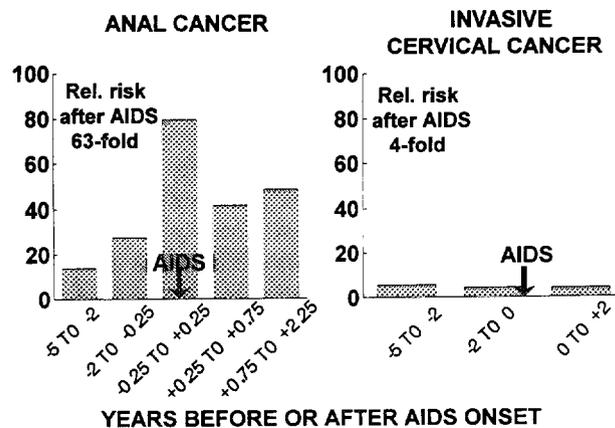


Figure 10 Changes in the relative risks of developing anal cancer in homosexual men (126) and cervical cancer in women in the pre-, at, and post-AIDS periods (149). For anal cancer, the high risk at AIDS is attributed to ascertainment bias. However, both the high relative risk and increasing relative risk as AIDS illness approached and past are consistent with anal cancer being related to HIV-infection or the related progressive deterioration of the immune system. However, there were no similar findings for cervical cancer in women. Prior screening and preventive care may have prevented a true association from being observed in women.

however. One might postulate that cervical cancer in Africa has a longer latent period than the expected survival from HIV-infection.

Contrary to the hypothesis that cervical cancer is unrelated to AIDS, the risk of epithelioid anal cancer, a condition also associated with HPV, is high in homosexual men with AIDS (123). Anal cancer was noted to be more frequent in homosexual men long before the AIDS epidemic appeared (22,124,125). However, the incidence rises as the HIV-infected population approaches and passes the time of AIDS (see Fig. 10), suggesting that it is related to the progression of immunosuppression (126). In contrast with cervical cancer, anal cancer risk does increase slightly among men approaching AIDS onset, even though it is a rare cancer (see Fig. 1; 2). Anal and cervical cancers appear to share major risk factors, including the associations with selected HPV types. These types are commonly found in sexually active homosexual men, with detection of HPV and findings of associated dysplastic lesions being more frequent in immunosuppressed men (127–129). Dysplastic lesions have not yet been reported to progress to invasive anal cancer, although the histological grade of the anal dysplastic lesions appears to increase over time in HIV-infected men (130), and disease progression may be only a matter of time. Despite these findings, anal cancer is not currently accepted as an AIDS-defining malignancy.

B. Hodgkin's Disease

Several reports indicate an increased frequency of Hodgkin's disease (HD) in patients with AIDS (2,131–133). Similarly, in a study linking 50,000 AIDS and cancer cases, there was an eight fold excess of HD, and the risk appeared to increase as AIDS onset was approached and passed (121). However, misclassification of NHL as HD occurred in up to 5% of NHL cases occurring in younger adults (134). Because the NHL excess is so high in AIDS, even a minor amount of erroneous classification either in the histology or the coding of NHL as HD would lead to a spurious association. In a very small series of followed-up reports, the histologies of 12 cases were reviewed at the National Institutes of Health, and 11 were confirmed to be HD (unpublished data). Therefore, it seems probable that HD is increased in AIDS.

Reported histological types are most commonly either mixed cellularity or, less commonly, lymphocyte-depleted (135). In non-HIV-infected persons nodular sclerosis is most common in young adults and only about 15% of HD will be of mixed cellularity or lymphocyte-depleted histological types (136). The presentation is at higher stages (80% have stage III or IV), and B symptoms (fever, weight loss, and night sweats) are more common in patients with AIDS (135,137). Mediastinal involvement appears to be infrequent (138). Given the advanced

stages, HD in HIV-infected can be difficult to treat, and survival is less than in persons without AIDS who acquire HD (137).

No etiology is known for HD. EBV can be detected in the majority (60–80%) of HD cases in AIDS patients, which is about twice the frequency seen in non-AIDS HD cases (137,138).

C. Leiomyosarcomas

Although very rare, the relative risk of leiomyosarcomas in children with AIDS is relatively high (139,140). This association has not been reported in adults with AIDS. This spindle cell sarcoma may involve the internal organs of the gastrointestinal tract and the lung, but it also occurs as a subcutaneous tumor. Malignant leiomyosarcoma and benign leiomyomas have both been associated with EBV in some (140,141), but not all (142), studies.

D. Conjunctival Tumors

Several reports from Africa have found higher than expected numbers of invasive conjunctival carcinomas in persons with AIDS (92,139,143). This tumor is rare in the United States, but is slightly more frequent than expected in AIDS cases (144,145). Some conjunctival tumors are HPV-infected, but this has not yet been confirmed for conjunctival tumors in persons with AIDS.

E. Testicular Cancer

Testicular tumor is relatively common in young men and, not surprisingly, it also occurs in men with HIV–AIDS. Seminomas are reported most commonly (50–70%; 146,147). However, registry-based studies have not supported the finding that there is an excess incidence of testicular cancers of any specific type (2,133). In one cohort study, a significant increase in testicular cancer was based on two gonadal cases and one extra gonadal case (148). In a large registry-linkage study, seminoma was significantly increased (relative risk 2.9-fold; 149). However, the lower 95% confidence limit was 1.1, and the increase became significant only by including cases of mediastinal seminoma. In summary, the evidence for an association with AIDS is currently of borderline significance, but it may well be confirmed.

F. Other Tumors

No other cancers have been firmly associated with HIV–AIDS, but a number are suspect. Because of its associations with hepatitis B and C, hepatoma incidence has been evaluated, but there is little to support an association in the United States

or in Africa, where the tumor is more frequent. Similarly, because of their EBV association, nasopharyngeal carcinomas were examined, but no significant excess was found (150). Lung cancer incidence was increased slightly (2), but excess smoking by HIV-exposure groups could be contributing. Nonmelanoma tumors of the skin and lip have been reported to be more frequent in persons with non-HIV-related immunosuppression (73,74,151,152), but the incidence has not been well evaluated in HIV–AIDS patients. Data about nonmelanoma skin cancer is often not collected by registries because variations in diagnosis and reporting make it unreliable. However, one report suggests that there might be an increased incidence, especially of basal cells types (153).

G. Summary

The striking aspect of AIDS is that the range of cancers occurring in excess is highly limited. The relation between KS and HIV–AIDS is extraordinary (100,000-fold increase), in part because KS is otherwise very rare in healthy young men. The background rate of NHL in young adults is higher, but HIV–AIDS patients have an excess risk of 150- to 200-fold. Other than KS and NHL (including primary brain lymphomas), only Hodgkin's disease is firmly HIV–AIDS-related, having an excess risk of eightfold, and leiomyosarcomas in children. Anal and cervical cancers could be related, but the evidence is still inconclusive. Certainly, they occur in excess, but whether the excess occurs because of HIV–AIDS and immunosuppression or because HIV-infected populations have other HPV-related risk factors is unclear. Testicular cancer may also be HIV–AIDS-related (threefold excess of borderline statistical significance).

Numerically, more KS cases have occurred in AIDS patients than NHL cases, but KS is a disease seen tenfold more frequently in homosexual men compared with other risk groups with AIDS. As homosexual men become a smaller proportion of new AIDS cases, the frequency of this disease in all AIDS patients will decline. However, NHL occurs equally frequently in HIV-exposure groups and this disease will not decline as a consequence of the changing distribution of AIDS exposure groups.

The frequency of these diseases is expected to change with the advent of new, highly active antiretroviral therapies (HAART; 154). If therapies were able to restore immunity to normal, presumably there would be no excesses of cancer. However, thus far, the improvements have been partial, rather than complete. There is evidence that existing KS can be reversed and the incidence of new KS declines in persons responding well to HAART (see Chapter 2). Thus far, however, no changes in the frequency of NHL have been observed, although there is preliminary evidence that the incidence of primary brain lymphomas may be declining. Analyses are only now beginning to be possible as sufficient numbers

of persons are being treated with HAART for periods long enough to observe changes in cancer incidence.

V. CANCERS ASSOCIATED WITH OTHER RETROVIRUSES OF HUMANS

Human Immunodeficiency Virus (HIV-2) is about 60% homologous with HIV-1. Infection causes a slowly progressive immunodeficiency condition. Laboratory studies have shown similar primate viruses can cause lymphomas in animals. In humans, NHL has been seen in HIV-2-infected persons, especially in autopsy material (155,156). However, the quantitative evidence is weaker because its distribution is confined to West Africa, where data about the distribution of HIV-2 and about cancer are both limited.

HTLV-I is also strongly associated with cancers, but of a very specific type: adult T-cell leukemia/lymphoma (ATLL). About 1–2% of HTLV-I-infected persons will develop ATLL during their lives (157). Some evidence suggested that infection early in life (mother-to-child transmission) is more likely to be associated with the later appearance of ATLL (158), implying that either the timing of infection is critical, or that the incubation period requires many years. HTLV-II has not been documented as causing cancers. HTLV-associated tumors have not been reported to occur excessively in persons coinfecting with HIV and HTLV.

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