

Human immunodeficiency virus infection, aging, and cancer

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Abstract

HIV infection increases non-Hodgkin's lymphoma and Kaposi's sarcoma risk. Among HIV-uninfected persons, risk for these malignancies and others increases with age. As HIV-infected persons age, new patterns in cancer incidence may emerge. In this article, data from the AIDS-Cancer Registry Match study are presented on risk for Kaposi's sarcoma and lung cancer among persons with AIDS. For 132,346 homosexual men with AIDS, Kaposi's sarcoma incidence was highest for men 30–39 years old (5.0 cases/100 person-years) and declined with age ($P_{\text{trend}} < .0001$). This trend likely arises from variation in Kaposi's sarcoma herpesvirus prevalence among homosexual men. For 239,257 adults with AIDS (all risk groups), lung cancer incidence increased with age, and was higher than in the general population ($P < .0001$), probably reflecting heavy smoking among HIV-infected adults. Identifying separate effects of HIV and aging on cancer risk will require detailed data on individuals' HIV infection status and exposures to known carcinogens. © 2001 Elsevier Science Inc. All rights reserved.

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1. Background

Persons infected with human immunodeficiency virus type 1 (HIV) have a very high risk for some tumors, most notably Kaposi's sarcoma and non-Hodgkin's lymphoma [1]. It is generally believed that HIV increases risk for these malignancies by destroying CD4-positive T lymphocytes and thereby profoundly damaging the host immune system. Risk for Kaposi's sarcoma is elevated because intact CD4 lymphocyte-mediated immunity is needed to control latent infection with Kaposi's sarcoma herpesvirus (KSHV), the viral cofactor for Kaposi's sarcoma. CD4 lymphocytes are also important for regulation of B lymphocytes, and their loss leads to the uncontrolled B lymphocyte proliferation seen in lymphomas.

HIV infection is associated with increased risk for only a few other types of malignancy [1]. Human papillomavirus-associated tumors, such as cancers of the cervix and anus, occur in excess among HIV-infected women and men. HIV may increase risk for these cancers by preventing immune-mediated clearance of early-stage lesions [2]. Alternatively, risk may be high merely because human papillomavirus infection is common in persons with high-risk

sexual behavior. Similarly, high rates of hepatocellular carcinoma and lung cancer might be due to the high prevalence of other key exposures (hepatitis B and C viruses, smoking) in persons with HIV, rather than to HIV-induced immunosuppression.

The incidence of many common cancers—for example, cancers of the lung, colon, breast, prostate, stomach, and bladder—increases with age in the general population. As discussed in more detail below, this age-related pattern can be explained by a “multistage” model for carcinogenesis, with cancer arising from precancerous cells with the acquisition of multiple genetic “hits” over time. Interestingly, of the six mentioned cancers associated with aging, only lung cancer is found increased in HIV infection, arguing against the notion that immunity is important in protecting against all types of cancer.

For HIV-infected individuals, there has previously been little opportunity to examine the effect of aging on risk for cancer, because most acquired infection as young adults, and their survival was poor. With the advent of highly active antiretroviral therapy in 1996, the prognosis of HIV infection and acquired immunodeficiency syndrome (AIDS) has improved markedly [3,4]. As a result, for the first time, many HIV-infected persons will be living as older adults. This fortunate occurrence raises two questions. First, will the aging of HIV-infected persons

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affect the incidence of *HIV-associated* cancers, especially Kaposi's sarcoma and non-Hodgkin's lymphoma? And second, will HIV increase the incidence of *aging-associated* cancers?

As examples of approaches to these questions, this article presents data on the age-specific risk for Kaposi's sarcoma and lung cancer in people with AIDS. The data come from the AIDS-Cancer Registry Match study which, as described in detail elsewhere [1,2], matched information on persons listed in AIDS and cancer registries in 11 U.S. regions (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). Using these methods, the study in its most recent update [2] identified malignancies occurring in over 300,000 persons with AIDS during the years 1980–1996. The included data are thus largely from before the era of highly active antiretroviral therapy. The example malignancies are common in persons with AIDS, and their presentation is selective and brief. Nonetheless, these examples illustrate application of the multistage model to cancers arising in HIV and highlight challenges that would arise in a

more complete analysis of the joint effects of HIV and aging on cancer risk.

2. Kaposi's sarcoma

The 1981 report of a previously rare skin tumor, Kaposi's sarcoma, occurring among young homosexual men in New York City and California heralded the worldwide HIV epidemic [5]. Among HIV-infected persons in developed countries, risk for Kaposi's sarcoma is highest for homosexual men and lower for others, such as intravenous drug users, heterosexual women, and hemophiliacs [6]. This differential risk parallels variation in KSHV prevalence, which is highest among homosexual men [7–10], possibly reflecting the spread of KSHV sexually or through exchange of saliva [11].

Before the HIV epidemic so strongly affected the epidemiology of Kaposi's sarcoma, the disease was seen in the developed world among elderly men (and to a lesser extent women) of Eastern European or Mediterranean origin ("classic" Kaposi's sarcoma) [12–15]. Patterns in KSHV prevalence somewhat mirror these KS rates (e.g., antibody

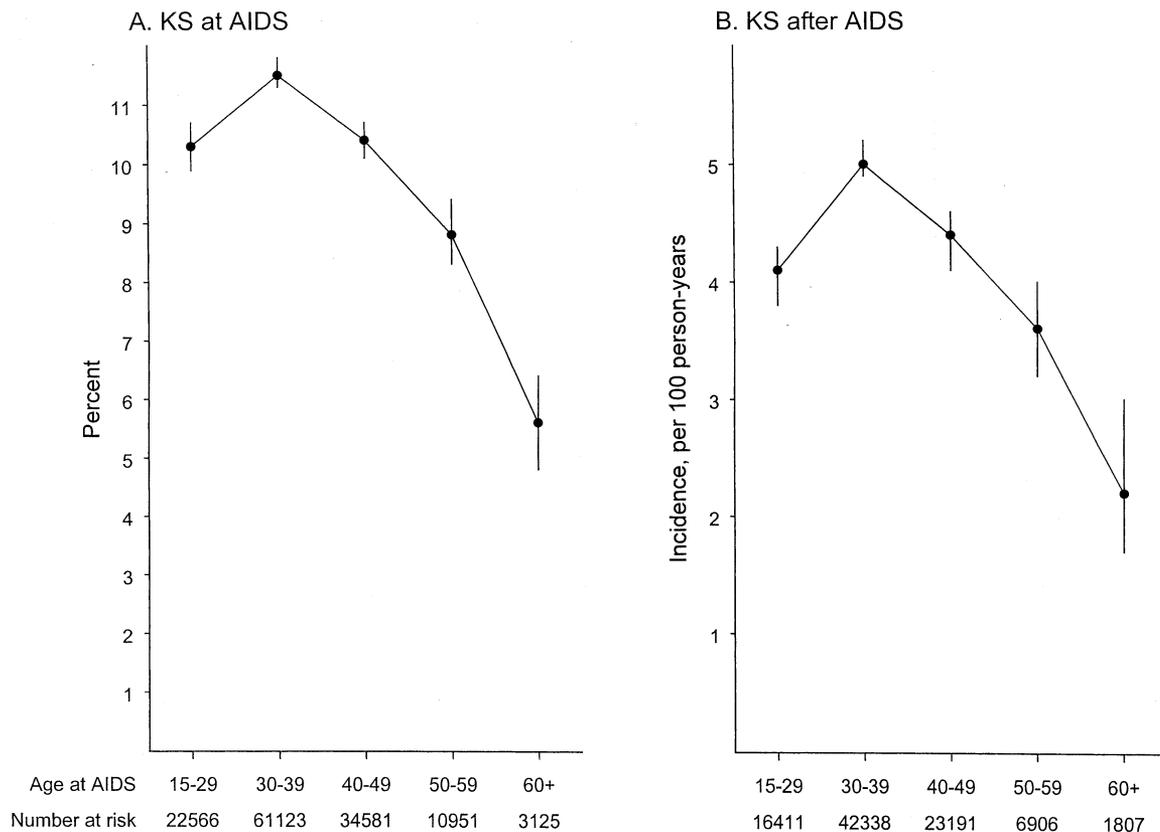


Fig. 1. Kaposi's sarcoma occurring in 132,346 homosexual men in the AIDS-Cancer Registry Match study, by age at AIDS diagnosis (in years). (A) This depicts the percentage of men with Kaposi's sarcoma in the AIDS period, defined as 0–3 months following AIDS onset. (B) This shows the incidence of Kaposi's sarcoma, per 100 person-years, in the 2-year period 4–27 months after AIDS onset, for men who did not previously have Kaposi's sarcoma and who survived to enter this 2-year period. Values are shown with 95% confidence intervals. The number of subjects in each age group is shown below the horizontal axis. Note that the vertical axis scale of (B) differs from that of Figure 2.

prevalence is high among Italian adults [16]). In the elderly, mild suppression or dysregulation of the immune system may contribute to loss of control of latent KSHV and lead to Kaposi's sarcoma [17].

Figure 1 presents age-specific data on 19,506 Kaposi's cases occurring among 132,346 homosexual men with AIDS. In the AIDS period (defined as 0–3 months after first AIDS diagnosis), 14,093 men (10.6%) developed Kaposi's sarcoma. As shown in Figure 1A, this proportion was highest for men who were 30–39 years old at AIDS onset (11.5%) and was lower for older men (e.g., 5.6% for men 60 years old or older at AIDS; $P_{\text{trend}} < .0001$ for ages above 30). In the 2 years after the AIDS period, 5,413 additional surviving homosexual men developed Kaposi's sarcoma (incidence 4.5 per 100 person-years). As shown in Figure 1B, Kaposi's sarcoma risk was again highest for men 30–39 years old at AIDS (incidence 5.0 per 100 person-years) and declined for older men ($P_{\text{trend}} < .0001$ for ages above 30).

This pattern (previously noted in an earlier match of AIDS and cancer registries [18]) obviously differs from the strictly increasing age-specific incidence seen for classic Kaposi's sarcoma in the HIV-uninfected population. Two explanations may underlie the observed peak at age 30–39 years. First, this pattern may largely be shaped by patterns in KSHV prevalence. For the years of the present study,

prevalence was extremely high in young homosexual men, with 25–35% having KSHV antibodies [8,9], probably as a result of infections acquired in the early 1980s [19]. Data on older homosexual men (born before 1935) are scant, but suggest KSHV prevalence might be lower [8,9] (and unpublished data). A second possible explanation, perhaps contributing to the lack of strictly increasing Kaposi's sarcoma risk with age, is that immune deficits associated with aging, although important for HIV-uninfected persons, are minor compared to the effects of HIV infection. For persons who have already developed AIDS, immune dysfunction may be equally severe regardless of age.

3. Lung cancer

For 239,257 adults (not restricted to homosexual men) surviving at least 3 months after AIDS onset, Figure 2 shows lung cancer incidence in the period 4–27 months after AIDS onset. In this population, incidence increased with age at AIDS, from 0.1 per 1,000 person-years for persons 15–29 years old, to 3.7 per 1,000 person-years for person 60 years old or older ($P_{\text{trend}} < .0001$). For comparison, Figure 2 shows lung cancer incidence in the portion of the general population matched to these study subjects by age, sex, race, and calendar year. Incidence also increased with age in the general population. Overall, incidence was higher in

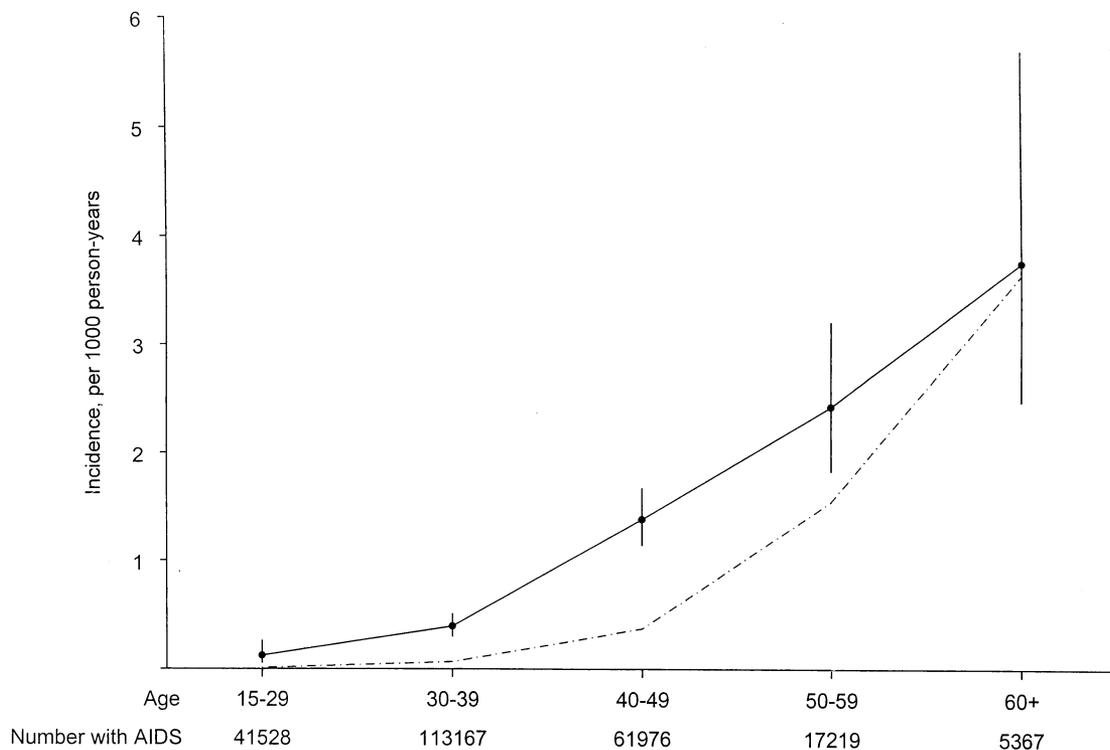


Fig. 2. Lung cancer occurring in 239,257 subjects with AIDS (all HIV risk groups), from the AIDS-Cancer Registry Match study, by age at AIDS diagnosis (in years). The solid line depicts incidence, per 1000 person-years, in the 2-year period 4–27 months after AIDS onset. Ninety-five percent confidence intervals for incidence estimates are also shown. For comparison, the dashed line shows lung cancer incidence in that portion of the general population matched to study subjects by age, sex, race, and calendar year. Note that the vertical axis scale differs from that of Figure 1(B).

persons with AIDS ($P < .0001$), with this difference especially notable for persons 30–59 years old (Fig. 2).

There are at least three possible explanations for the elevated incidence of lung cancer in persons with AIDS. First, HIV-infected persons likely smoke more, on average, than HIV-uninfected persons. This is plausible given the relatively high prevalence of HIV infections in groups (e.g., intravenous drug users, homosexual men) in which smoking is common [20]. Unfortunately, registries do not record information on individuals' smoking status. One might attempt to derive from registry data an estimate of the effect of HIV on lung cancer risk, adjusted for the use of tobacco, but such an approach would rely on an ecological analysis and would thus be problematic [21]. Second, the pattern in Figure 2 may be partly due to screening bias. People with AIDS are under active medical care, and could receive diagnostic radiographs that detect asymptomatic malignancies at an unusually early stage. Third, it is possible that HIV itself has a facilitating effect on development of lung cancer, perhaps by eliminating immune surveillance against early lesions. Arguing against these last two possibilities, however, the spectrum of lung cancer types and stages at diagnosis is similar in persons with and without HIV infection [22].

4. Discussion

Consideration of a general model for cancer etiology (the "multistage" model) can inform interpretation of these examples and place the roles of immunosuppression and aging into context. This widely accepted model, first proposed by Armitage and Doll in 1954 [23], posits that malignancies arise following a series of stages. The completed passage of a cell through these stages results in the uncontrolled cellular proliferation that manifests clinically as a malignancy. Nonetheless, cancer is a heterogeneous syndrome, and etiology varies by site and histology. For example, the causes of non-Hodgkin's lymphoma may differ from those for lung cancer, and the causes of small cell lung cancer may differ from those for nonsmall-cell lung cancer. For each type of malignancy, there may be multiple pathways by which the tumor arises. Furthermore, in the framework of this model, the stages in each pathway correspond to specific changes in a cell's genetic information ("hits"), which arise as the result of tumor-specific exposures.

Hits to cellular genetic information can occur in several ways. Rarely, they are caused by inborn genetic mutations. Other hits are caused by the damaging effects of specific environmental exposures, such as radiation or tobacco smoke. Viruses, as a type of environmental exposure, can supply hits in a unique manner, by inserting their own genetic material into a vulnerable cell. For example, hepatitis B virus DNA can integrate into a hepatocyte's chromosomal material, which might thereby lead to hepatocellular carcinoma by disrupting key human genes [24]. Viruses can act indirectly by interfering with normal cellular processes and promoting cellular genetic error. For instance, hepatitis C virus

probably increases risk for hepatocellular carcinoma by inducing chronic hepatocellular damage and regeneration, which can then lead to mutation in a human gene [24].

HIV probably affects cancer risk indirectly, through immune suppression, rather than by itself supplying or causing genetic hits. HIV-induced loss of CD4-mediated cellular immune function prevents control or elimination of specific premalignant conditions: latent infection with KSHV (Kaposi's sarcoma), aberrant proliferation of B lymphocytes (non-Hodgkin's lymphoma), and perhaps epithelial cells infected with human papillomavirus (cervical and anal cancers). These persisting premalignant conditions then provide the necessary substrate for subsequent stages in the causal pathway to cancer.

The increasing risk with age for many malignancies has a simple explanation under the multistage model: the age-specific rates of necessary exposures affect the age-specific rates of cancer [23,25]. For example, risk for cervical cancer becomes appreciable only after adolescence, the period during which human papillomavirus is acquired sexually. Furthermore, although some exposures such as human papillomavirus infection are common, the genetic hits that they induce, needed for development of cancer, may be rare, and to some extent randomly determined. Hits might occur only after intense or prolonged exposure. Because tumors arise only with the acquisition of successive hits, cancer incidence increases only after a prolonged period, i.e., with aging. Aging also impairs immune function [26], although to a much smaller degree than does HIV infection, and is associated with increased incidence of Kaposi's sarcoma and non-Hodgkin's lymphoma among HIV-uninfected persons. Under the multistage model, it is not necessary to posit an effect of aging per se (e.g., deterioration of tissues with age) on cancer risk [25].

To understand whether HIV or aging increase the risk of malignancy through the mechanisms discussed above, information on the prevalence, duration, and intensity of other key exposures is required. For instance, exposure to tobacco smoke is common among persons with HIV, and the frequency and duration of exposure increases with age. These considerations together, absent effects of HIV or aging per se, might explain the patterns in lung cancer incidence seen in Figure 2. Infections with some carcinogenic viruses (KSHV, hepatitis B and C viruses, human papillomavirus) are especially common in HIV-infected persons due to shared routes of acquisition. Lack of control for confounding by these exposures can lead to erroneous attribution of increases in risk to HIV or aging itself.

As we move into a new "treatment" era of HIV infection, several time-related trends will affect cancer incidence in complex ways. First, individuals who have survived with HIV from earlier years will be aging, so they will be older, on average, than persons living with HIV in the 1980s and 1990s. Second, because of the passage of time, these older adults might be more immunosuppressed than older adults in previous years. Increasing prevalence of carcinogen exposure

with aging and increased immunosuppression with duration of HIV infection might lead to increases in cancer risk. On the other hand, many HIV-infected older adults should be considered long-term “survivors,” given that they have survived for 1–2 decades with HIV infection, and they might have genetic traits that actually reduce their risk for HIV-related immunosuppression and its complications, including cancer. Additionally, older adults today will likely have had more exposure to HIV therapy than older adults in earlier years, which could affect cancer risk in unknown ways.

Finally, the time course of other epidemics may introduce cohort effects that will strongly shape cancer incidence. There is evidence for an explosive epidemic of KSHV infection among homosexual men in the early 1980s [8,19]. Among HIV-infected homosexual men, differences in KSHV prevalence by age could reflect participation in this second epidemic and partly account for observed patterns in Kaposi’s sarcoma risk (Fig. 1). In the future, age-specific patterns in Kaposi’s sarcoma incidence will be affected by the aging of persons already infected with KSHV and the occurrence of new KSHV infections among HIV-infected individuals.

The aging of HIV-infected individuals provides the opportunity to address the two questions posed in the introduction. Some cancers may become more common among HIV-infected persons. However, as the examples and discussion highlight, it is conceivable that HIV infection and aging would not themselves be responsible for the increased risk for most of these cancers. To an epidemiologist interested in better understanding cancer etiology, the questions might best be reformulated as, “Will aging of HIV-infected persons affect the incidence of HIV-associated cancers (Kaposi’s sarcoma and non-Hodgkin’s lymphoma), *after controlling for* the duration of HIV infection, level of immune suppression, and prevalence of key carcinogens (e.g., KSHV)?,” and, “Will HIV increase the incidence of aging-associated cancers, *after controlling for* the prevalence, duration, and intensity of exposure to key carcinogens (e.g., tobacco)?” Addressing these questions will likely require detailed data on the course of individuals’ HIV infection and their exposures to a variety of other known agents. Conducting rigorous studies that gather such information will be complex, and pose demanding challenges to epidemiologists embarking on the next generation of research on HIV, aging, and cancer.

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