



Evolving epidemiology of HIV-associated malignancies

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Purpose of review

The purpose of this review is to describe the epidemiology of cancers that occur at an elevated rate among people with HIV infection in the current treatment era, including discussion of the cause of these cancers, as well as changes in cancer incidence and burden over time.

Recent findings

Rates of Kaposi sarcoma, non-Hodgkin lymphoma and cervical cancer have declined sharply in developed countries during the highly active antiretroviral therapy era, but remain elevated 800-fold, 10-fold and four-fold, respectively, compared with the general population. Most studies have reported significant increases in liver cancer rates and decreases in lung cancer over time. Although some studies have reported significant increases in anal cancer rates and declines in Hodgkin lymphoma rates, others have shown stable incidence. Declining mortality among HIV-infected individuals has resulted in the growth and aging of the HIV-infected population, causing an increase in the number of non-AIDS-defining cancers diagnosed each year in HIV-infected people.

Summary

The epidemiology of cancer among HIV-infected people has evolved since the beginning of the HIV epidemic with particularly marked changes since the introduction of modern treatment. Public health interventions aimed at prevention and early detection of cancer among HIV-infected people are needed.

Keywords

aging, cancer, epidemiology, HIV, immunosuppression, rates

INTRODUCTION

Cancer has been a major feature of the HIV epidemic from the beginning, when cases of Kaposi sarcoma and non-Hodgkin lymphoma (NHL) were among the first reported manifestations of what later came to be known as AIDS [1–3]. Moreover, despite marked improvements in HIV treatment and outcomes, cancer continues to comprise a sizeable part of the disease burden and mortality attributable to HIV infection [4,5,6,7]. Research on the epidemiology of cancer among HIV-infected people provides important information to help public health professionals, clinicians and patients optimize overall health outcomes in the HIV population. This research is also informative with respect to the etiologic contribution of immunosuppression, viral infections and inflammation to the development of malignancies.

The present review describes some major features of the epidemiology of cancer among HIV-infected people. As we discuss below, there have

been some notable changes over the 35-year course of the HIV epidemic. We focus on the most common cancers that are elevated in incidence among HIV-infected people, characterize recent trends and highlight the patterns for developed countries, because most data on HIV and cancer have been collected from large cohort and registry-based studies in the USA, Europe and Australia. Nonetheless, much of what has been learned regarding HIV and cancer in developed countries can be applied to developing countries, and we also briefly discuss

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KEY POINTS

- People with HIV have an elevated risk of a number of cancer types, including AIDS-defining cancers (Kaposi sarcoma, NHL and cervical cancer) and selected non-AIDS-defining cancer (e.g. anal cancer, liver cancer, Hodgkin lymphoma and lung cancer).
- In developed countries, rates of AIDS-defining cancers have declined since the introduction of HAART in 1996.
- Most studies report increases in liver cancer and decreases in lung cancer rates in the HAART era. Although some studies have reported increases in anal cancer rates and decreases in Hodgkin lymphoma rates over time, others have reported no change in incidence.
- Because of the growth and aging of the HIV-infected population in the USA, the number of non-AIDS-defining cancers diagnosed in this population is growing each year.
- Public health interventions aimed at the prevention and early detection of cancer are needed to reduce the impact of cancer among HIV-infected people.

the epidemiology of HIV and cancer in Africa, where most HIV-infected people live.

AIDS-DEFINING CANCERS

HIV-infected individuals have a substantially elevated risk of developing Kaposi sarcoma, certain high-grade NHLs and cervical cancer [8,9], all of which are considered AIDS-defining cancers, that is they mark the onset of clinically relevant immunosuppression. In the United States during 1991–1995 [before the introduction of highly active anti-retroviral therapy (HAART) in 1996], HIV-infected people had risks that were 2800-fold elevated for Kaposi sarcoma, 10-fold elevated for NHL and three-fold elevated for cervical cancer compared with the general population [8]. Because of the extraordinary elevation in Kaposi sarcoma risk, the majority of Kaposi sarcoma cases in the United States during the pre-HAART era were among HIV-infected people [10]. NHL is a heterogeneous entity, and risk among HIV-infected people is most strongly elevated for the three AIDS-defining subtypes, namely, diffuse large B-cell lymphoma, Burkitt lymphoma and central nervous system lymphoma [11].

The three AIDS-defining cancers are all caused by viruses: Kaposi sarcoma-associated herpesvirus (KSHV) for Kaposi sarcoma, Epstein–Barr virus (EBV) for most cases of the lymphomas closely linked to HIV and human papillomavirus (HPV)

for cervical cancer. One contribution to the high risk among HIV-infected people is the high prevalence of viral coinfection with KSHV [which is transmitted sexually, especially among men who have sex with men (MSM)] and HPV (which is transmitted sexually among both men and women). For Kaposi sarcoma and NHL, the high risk is also strongly related to advancing immunosuppression, as manifested by declines in circulating CD4 cell counts [12]. The elevated risk of cervical cancer in HIV-infected women is partly due to increased sexual acquisition of HPV and incomplete use of preventive screening. Nonetheless, HIV-infected women are less likely to clear cervical HPV than HIV-uninfected women, and some data support that risk of cervical cancer increases with declining CD4 cell count [12,13]. Thus, epidemiologic evidence points to an etiologic model whereby the AIDS-defining cancers arise through loss of immunologic control of oncogenic viral infections.

NON-AIDS-DEFINING CANCERS

HIV-infected people also have an elevated risk for some of the remaining ('non-AIDS-defining') cancers, some of which are also caused by viral infections. Anal cancer is caused by HPV. Risk for this cancer is strongly elevated among HIV-infected people, particularly among MSM, who are likely to acquire anal HPV infection through sexual intercourse. During the pre-HAART era in the United States, MSM with AIDS manifested an approximately 90-fold increase compared with men in the general population [14]. Risk is also elevated for Hodgkin lymphoma, especially for cases linked to EBV [8,9]. Advancing immunosuppression contributes to risk for both anal cancer and Hodgkin lymphoma, although the relationships appear to be more complex than for Kaposi sarcoma and NHL [15,16]. Liver cancer is also elevated among HIV-infected individuals [8,9,17], in large part related to a high prevalence of coinfection with hepatitis B and C viruses (HBV and HCV), which are transmitted sexually and via blood-borne routes (e.g. injection drug use). Immunosuppression appears to increase risk for HBV-related liver cancer, whereas the importance of immunosuppression in HCV-related cases is less clear [18].

HIV-infected people also have an increased risk of lung cancer. In developed countries during the pre-HAART era, lung cancer risk was 3–5-fold elevated in HIV-infected individuals compared with the general population [8,9,19]. This increase partly reflects a very high prevalence of tobacco use [20²²], and lung cancer cases that do arise are almost entirely among current or former smokers

[21]. However, the elevation in lung cancer appears higher than can be explained by smoking alone [19,21,22]. Repeated lung infections, chronic pulmonary inflammation and/or immunosuppression may act synergistically with tobacco to promote the development of lung cancer [12,23]. In contrast, HIV-infected people do not have an elevated risk for other common malignancies such as colorectal, prostate and breast cancers [8,9]. Indeed, for unclear reasons, the rates of prostate and breast cancers are significantly reduced among HIV-infected people compared with the general population.

HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

The availability of HAART in developed countries beginning in 1996 has greatly changed the clinical outlook for HIV-infected people and has had a dramatic public health impact [24–26]. The use of HAART allows for prolonged suppression of HIV replication and improved immune status, as manifested in rising CD4 cell counts. The widespread use of HAART at the population level has also sharply reduced the incidence of AIDS and overall mortality among HIV-infected people [24–26]. Given the strong effects on immune status and longevity, it is therefore not surprising that HAART has had a major effect on the epidemiology of cancer among HIV-infected people.

TRENDS IN CANCER INCIDENCE RATES IN THE HIGHLY ACTIVE ANTIRETROVIRAL THERAPY ERA

In the early HAART era, rates of Kaposi sarcoma declined 60–70% and rates of NHL declined 30–50% in HIV-infected people in the United States compared with the time period immediately preceding 1996, whereas rates of cervical cancer remained stable [27,28]. More recent data from studies of HIV-infected people in the United States, Europe and Australia have shown continued declines in incidence rates of Kaposi sarcoma and NHL, as well as declines in cervical cancer rates [29–32]. In the United States, data from the HIV/AIDS Cancer Match (HACM) Study showed average yearly declines in incidence rates of 6% for Kaposi sarcoma during 2000–2010, 5% for NHL during 2003–2010 and 12% for cervical cancer during 1996–2010 (Fig. 1a) [29]. Despite dramatic decreases in rates of AIDS-defining cancers, rates of Kaposi sarcoma, NHL and cervical cancer remain elevated 800-fold, 10-fold and four-fold, respectively, compared with the general population [29]. A consortium of North American cohorts estimated that in the HAART era, the probability of developing cancer (i.e. cumulative incidence) by age 65 among HIV-infected people was 4% for both Kaposi sarcoma and NHL, though the cumulative incidence declined significantly across 1996–2009 [33²²].

Incidence rates of some non-AIDS-defining cancers have also changed during the HAART era. In the HACM Study, anal cancer rates increased 3% per

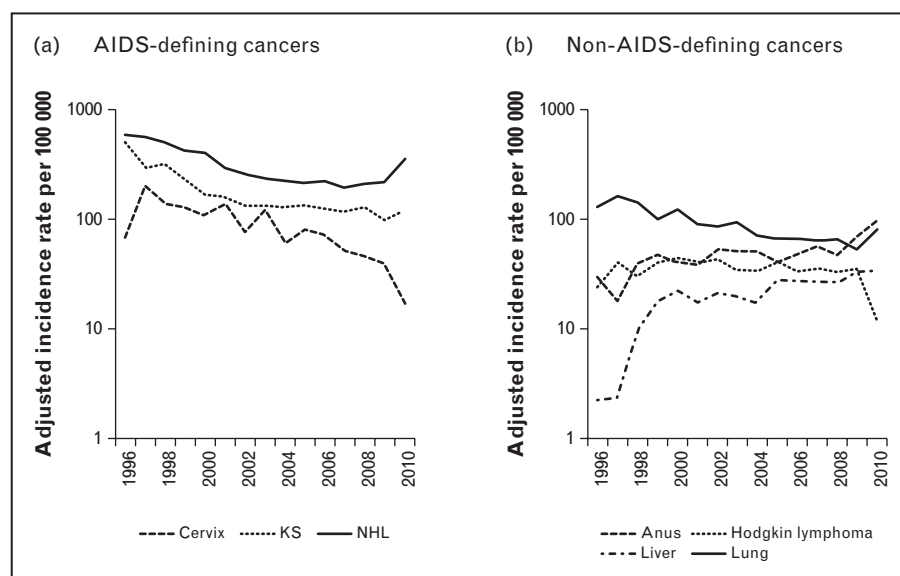


FIGURE 1. Time trends in incidence rates of (a) AIDS-defining cancers (Kaposi sarcoma, non-Hodgkin lymphoma and cervical cancer); and (b) non-AIDS-defining cancers (anal cancer, liver cancer, Hodgkin lymphoma and lung cancer). Rates were estimated with data from the HIV/AIDS Cancer Match Study and standardized to the 2002 HIV population by age, sex, HIV risk group, race/ethnicity and time since HIV/AIDS registration. Figures were generated with data from Robbins *et al.* [29].

year during 1996–2010 [29] (Fig. 1b), reflecting increasing rates in the general United States population [29], whereas other studies reported no change in incidence rates over time or increases only among women [30,31,34,35]. Most studies reported significant increases in liver cancer rates over time (6% per year in the HACM Study) [10,29,34], and significant decreases in lung cancer rates (–6% per year) (Fig. 1b) [22,29,31,34], though other studies reported no changes in the rates of these cancers over time [30,35]. Decreasing rates of Hodgkin lymphoma were reported in some studies (–3% per year in the HACM Study) (Fig. 1b) [17,29], whereas another study reported a 50% decline in Hodgkin lymphoma rates from 1997–2000 to 2001–2004 followed by a flat trend [32], and others observed no significant change over time [34,35]. In the United States during 2006–2010, HIV-infected people continued to have elevated rates for anal cancer (32-fold elevation compared with the general population), lung cancer (two-fold), liver cancer (three-fold) and Hodgkin lymphoma (10-fold) [29]. In the HAART era, the probability of HIV-infected people in North America developing these cancers by age 65 was 1.3% for anal cancer, 2.2% for lung cancer, 0.8% for liver cancer and 0.9% for Hodgkin lymphoma [33[■]].

CANCER BURDEN IN HIV-INFECTED PEOPLE

With the longevity afforded by modern treatment, a 20-year-old person infected with HIV today now has a projected life expectancy that is similar to that observed in the general population [36]. Declines in mortality among HIV-infected individuals have resulted in the growth and aging of the HIV-infected population, which has implications for current and future cancer risk and the total burden of cases. In the United States, the number of people living with AIDS more than doubled from 242 000 in 1996 to 516 401 in 2013 (Fig. 2) [4], and the entire HIV-infected population increased from 818 638 in 2008 to 933 941 in 2013 (United States nationwide estimates are only available for all HIV-infected people in the most recent years) [37–39]. Further, the age distribution of people living with HIV has shifted to older ages over time. For example, in 1996, 2.5% of people with AIDS in the United States were at least 60 years old, compared with 15.4% in 2013 [38].

Because cancer risk increases with age, and the HIV population is growing, the burden of HIV-infected people with cancer has also grown markedly. One prior United States study, focused on people with AIDS, estimated changes in the cancer burden over time, and found that while the number of cases

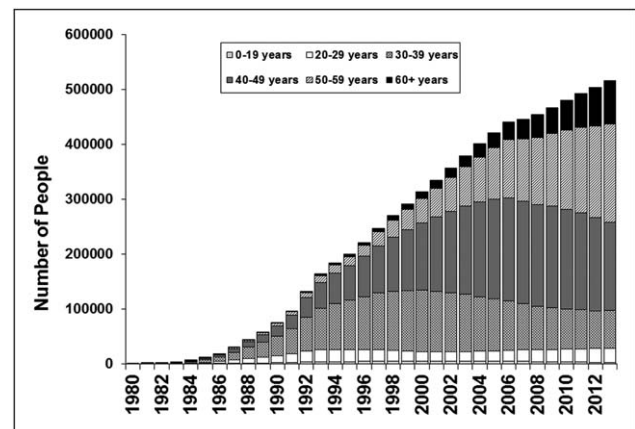


FIGURE 2. People living with AIDS in the United States, 1996–2013. Colored segments of each bar represent the number of people in each age group. Data were provided by the United States Centers for Disease Control and Prevention. Figure is an updated version of a figure published in Shiels *et al.* [4].

of Kaposi sarcoma and NHL has declined over time (driven by the sharply decreasing incidence rates), the total number of cases for each non-AIDS-defining cancer increased over time, largely driven by the growth and aging of the HIV population, as well as increasing cancer rates for some sites [4]. This pattern was seen for both non-AIDS-defining cancers that are elevated among people with HIV (e.g. anal and lung cancers) and cancers that are common in the general population but do not occur more frequently in people with HIV (e.g. breast and prostate cancers). The total number of non-AIDS-defining cancers has exceeded the number of AIDS-defining cancers since 2003 among people with AIDS, highlighting the changing spectrum of cancers diagnosed in this population (Fig. 3) [4]. In the United States in 2010, the most common cancers diagnosed among HIV-infected people were NHL ($n=1650$; 21% of incident cancer cases) and Kaposi sarcoma ($n=910$; 12%), but these were followed closely by lung cancer ($n=840$; 11%), anal cancer ($n=760$; 10%) and prostate cancer ($n=570$; 7%) [5[■]]. As the HIV-infected population continues to grow and age, the burden of cancer (particularly non-AIDS-defining cancers) will continue to rise, as will the need for cancer prevention, early detection and treatment.

HIV AND CANCER IN THE DEVELOPING WORLD

In sub-Saharan Africa, where a large proportion of all HIV-infected people reside, Kaposi sarcoma and cervical cancer are among the most common cancers [40,41]. As in developed countries, risk for all three AIDS-defining cancers is elevated among HIV-

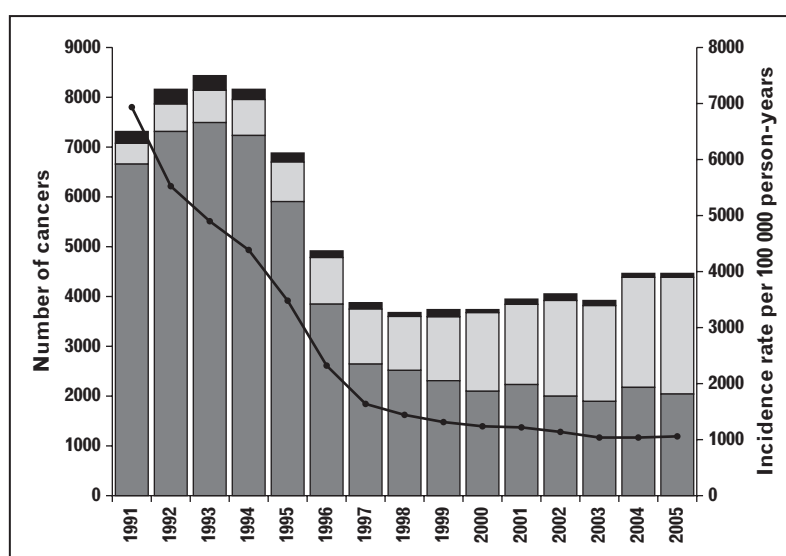


FIGURE 3. Total number of cancer cases (i.e. cancer burden) among people with AIDS in the United States, 1990–2005. Bars represent the total number of cases occurring in each year, stratified by type of cancer (left axis). Dark gray bars represent AIDS-defining cancers, light gray bars represent non-AIDS-defining cancers and black bars represent poorly specified cancers. Points connected by lines represent overall cancer incidence rates, standardized by age group, race and sex to the 2000 AIDS population in the United States (right axis). The figure was previously published in Shiels *et al.* [4].

infected people in Africa [42–44], and the onset of the HIV epidemic led to a dramatic increase in Kaposi sarcoma incidence [45]. The greatly expanding access to HAART in recent years, made possible through international assistance programmes, will hopefully lead to a reduction in the incidence of AIDS-defining cancers over time. Most African countries lack population-based cancer registry data that allow an assessment of cancer burden. Nonetheless, analyses of incidence data from cancer registries in Uganda and Botswana provide evidence for recent declines in Kaposi sarcoma that are temporally associated with uptake of HAART [46,47].

CONCLUSION

The epidemiology of cancer among HIV-infected people has evolved since the beginning of the HIV epidemic, tracking strong patterns in cancer incidence rates and dynamic population demographics preceding and following the introduction of modern HIV treatment. However, much more epidemiologic research is needed. Little information is known yet about cancer risks among people living with HIV for decades. Studies must continue to monitor cancer rates over time in the HIV-infected population, and estimates of future rates and burden are needed to identify targets for cancer prevention and early detection, as well as to guide resource allocation. Further, more information is needed on the risk of cancer among HIV-infected people living in the developing world, particularly in Africa, where the HIV epidemic

is most concentrated. Large, population-based studies in many of these countries are difficult because of the lack of national and regional registration of HIV and cancer, and resources and expertise in disease surveillance are needed.

Finally, public health interventions aimed at the prevention and early detection of cancer are needed to reduce cancer risk among HIV-infected people. Current guidelines recommend that all HIV-infected people receive treatment with antiretroviral therapy [48]. Increasing the fraction of people in care could further decrease rates of NHL and Kaposi sarcoma. Additional public health interventions such as smoking cessation programmes and treatment of HBV and HCV could also reduce the cancer burden in this population. For most cancer sites, HIV-infected individuals should follow the same age-based screening guidelines as the general population, though separate guidelines have been issued for Pap testing for the prevention of cervical cancer in HIV-infected women [49], and a clinical trial is currently assessing the utility of Pap testing and treatment of precursor lesions for anal cancer prevention in HIV-infected men and women (NIH clinical trials identification number: NCT02135419).

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Conflicts of interest

There are no conflicts of interest.

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