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Authors
Wang, Chia-ching J
Silverberg, Michael J
Abrams, Donald I

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Non-AIDS-Defining Malignancies in the HIV-Infected Population

Chia-ching J. Wang, MD[1], **Michael J. Silverberg, MPH, PhD**[2], and **Donald I. Abrams, MD**[3]

[1]Division of Hematology/Oncology, Helen Diller Comprehensive Cancer Center, University of California, San Francisco

[2]Division of Research, Kaiser Permanente Northern California, Oakland, California

[3]Division of Hematology/Oncology, San Francisco General Hospital, University of California San Francisco

Abstract

With the advent of effective combination of antiretroviral therapy, HIV infection has been transformed from a fatal disease to a chronic condition. There is renewed clinical interest in long-term morbidities, including malignancies that occur disproportionately within this population. Non-AIDS-defining cancers (NADCs) represent a significant source of morbidity and mortality in the aging HIV-infected population. There is data to suggest that incidence rates are elevated among HIV-infected individuals for many cancer sites, particularly those with a confirmed or suspected infectious etiology. The complex interplay between behavioral risk factors, co-existence of viral infections, immunodeficiency and antiretroviral therapy makes it difficult to analyze why certain cancers developed more frequently in HIV-infected individuals. The challenge to clinicians caring for HIV-infected patients is to develop and implement effective means to screen, treat, and prevent NADCs in the future. This review presents data on whether NADCs are increased in the HIV-Infected population, as well as ongoing research on epidemiology, prevention and pathogenesis of this evolving aspect of the HIV epidemic.

Keywords

HIV/AIDS; cancer; epidemiology; lung cancer; human papilloma virus; head and neck cancer; anal cancer; hepatitis; hepatocellular carcinoma; Hodgkin lymphoma

Correspondence to: Chia-ching J. Wang.

Chia-ching J. Wang (corresponding author), University of California, San Francisco, Division of Hematology/Oncology, 505 Parnassus Avenue, Box 1270, San Francisco, CA 94143, Telephone 415-476-1000 Fax 415-476-0624 chia-ching.wang@ucsf.edu.
Contact information:
Michael J. Silverberg, Kaiser Permanente Division of Research, 2000 Broadway, Oakland, CA 94612, Telephone 510-891-3801 Fax 510-891-3508 Michael.J.Silverberg@nsmtp.kp.org
Donald I. Abrams, 995 Potrero Avenue, SFGH Building 80, Room 425, San Francisco, CA 94143, Telephone 415-206-4919 Fax 415-502-2991 dabrams@hemeonc.ucsf.edu

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the author.

Conflict of Interest

Donald Abrams declares no conflicts of interest.

Introduction

Infection with HIV increases the risk for certain types of cancer. The risk for Kaposi sarcoma and non-Hodgkin's lymphoma (NHL) is significantly greater among HIV-infected persons; therefore these types of cancer are included in the Centers for Disease Control and Prevention's definition of AIDS-defining conditions [1]. Invasive cervical cancer was added to this list of conditions in 1993 not simply for increased prevalence but also because HIV infection may adversely affect its clinical course and treatment. More recently, it has been suggested that persons with HIV infection develop non–AIDS-related types of cancer more frequently than the general population [2–6]. This may be explained by multiple mechanisms, which include improvement in life expectancy with antiretroviral therapy [7–9], premature aging [10–11], loss of control of oncogenic infections due to HIV-related immune suppression [12–13] and a high prevalence of exposure to other carcinogens such as tobacco or alcohol [2, 14].

Since an exhaustive review of HIV and its impact on risks for all malignancies cannot be easily done, infection-related non-AIDS defining cancers, lung cancer and Hodgkin lymphoma have been selected for their strength of association with HIV. In addition to age, traditional risk factors (such as tobacco use), immunodeficiency and chronic viral co-infections all contribute to increase of incident cancer rates in the HIV-infected population, and influence prevention and screening of these malignancies.

Epidemiology of non-AIDS-defining Cancers (NADC)

The use of highly active antiretroviral therapy (HAART) has dramatically improved survival among HIV-infected persons and decreased the incidence of AIDS. Shortly after the advent of HAART, mortality rate for those infected with HIV declined by at least 40% [7–9]. The HIV-infected population in the US expanded fourfold from 1991 to 2005 largely because of an increase in the number of people with HIV aged 40 years or older [15]. As a result, by the end of 2009, approximately 1.1 million persons in the United States were living with HIV/AIDS [16]. From 2008 through 2010, the prevalence of HIV/AIDS increased by 26% among persons aged 65 and older [16]. By 2015, more than half of people living with HIV/AIDS in the US will be more than 50 years of age [11]. Notably, a 20-year-old HIV-infected adult on ART in the US or Canada is expected to live into their early 70's, a life expectancy approaching that of the general population [17]. Therefore, attention must be paid to health maintenance measures, including age appropriate cancer screening, for the growing HIV-infected population; and understanding underlying epidemiology for those malignancies is paramount to establish screening guidelines.

Despite its unquestioned success in prolonging survival for those infected with HIV, HAART does not fully restore health. For reasons that remain poorly defined, long-term treated HIV-infected persons have an expected life span that is still shorter than their HIV-uninfected peers [18, 19]. This shortened life span is largely due to an increased risk of a number of non-AIDS complications, including cardiovascular disease, liver disease, kidney disease, bone disease, and neurocognitive decline [20]. Many of these complications are

similar to those observed among the elderly. These observations have led to growing concern that HIV-infected persons suffer from accelerated or premature aging.

With a few exceptions, cancer is primarily a disease of aging. Understandably, the burden of cancer, particularly NADCs, is likely to increase as HIV-infected persons live longer. From 1991–1995 to 2001–2005, the estimated number of NADCs increased by approximately threefold, whereas number of AIDS-defining cancers decreased by greater than threefold [15]. When Yanik et al evaluated the incidence and timing of cancer diagnoses among patients initiating ART between 1996 and 2011 in a collaboration of 8 US clinical HIV cohorts, they found that incidence rates for all NADCs combined increased from 1 to 10 years after ART initiation (average 7% increase per year; 95% confidence interval, 2%–13%) [21]. Data from the Veterans Affairs Healthcare System demonstrated that the incidence of NADCs is higher among HIV-infected than HIV-uninfected patients, even after adjusting for age, race, and gender [22]. In addition, median CD4 counts were lower for those with NADCs, anal cancer, and Hodgkin lymphoma among HIV-infected patients in this cohort. The French Hospital Database also found that current CD4 was the most significant predictive factor for all malignancies except anal cancers [23]. These findings highlight the importance of ongoing aggressive cancer screening and prevention efforts throughout the course of HIV care.

For cancer, premature aging could manifest not only as an overall elevated cancer risk but also as a downward shift in the distribution of ages at cancer diagnosis. Earlier studies of lung [24–26], liver [27–28], anal [29], and colorectal cancer [30] have noted ages at diagnosis that are 10 to 20 years younger among persons with HIV compared with the general population. However, HIV tends to be acquired at a young age and persons with HIV have shorter life expectancy than those without HIV. As a result, the proportion of persons with HIV who are older is far smaller than in the general population. For example, in the United States in 2010, only 4% of HIV-infected persons were aged 65 years or older [16], compared with 13% of the general population [31]. Because overall cancer incidence is 10 times higher in persons aged 65 years or older than in persons younger than 65 years [32], the truncated age distribution among persons with HIV precludes observation of most instances of cancer that would occur at older ages, which could explain the dramatic age differences at the time of cancer diagnosis reported in previous studies.

Notably, the HIV Cancer Match Study showed that although modest age differences remained for lung cancer, anal cancer and Hodgkin lymphoma, the median ages at diagnosis in the AIDS and general populations did not differ for most types of cancer (e.g. colon, prostate, or breast cancer) after adjustment for differences in the age-structure of populations at risk [33]. These findings do not support premature aging in HIV-infected persons. As the HIV/AIDS population continues to age, more cases of NADCs will be expected to occur at older ages, which would attenuate or eliminate the apparent age differences at cancer diagnosis.

Infection-Related Cancers

Substantially greater risk of cancers with a known infectious cause in HIV-infected persons compared with HIV-uninfected persons has been demonstrated in multiple studies. Infection-related cancers (including AIDS-defining cancers) comprised almost 70% of all cancers in HIV-infected persons enrolled in an integrated healthcare system in California compared with only 12% in HIV-uninfected persons of similar age and sex [12]. In this cohort, HIV-infected persons had a more than nine-fold increased risk of infection-related NADC compared with HIV-uninfected persons, which was largely influenced by differences in the risk of anal squamous cell cancer.

Viral co-infections including human papillomavirus (HPV) [34], hepatitis B and C [35] are common in HIV-infected persons. The suppressed immune system of HIV-infected persons reduces the ability to control oncogenic viral process, which could explain the greater risk of infection-related cancer in the HIV-infected population. This hypothesis is supported by a large meta-analysis by Grulich et al. [13] who compared cancer incidences in population-based cohort studies of persons with HIV infection and organ transplant recipients. Many cancers that occurred with higher frequencies in both populations compared with the general population had a known or suspected infectious cause. Since these two populations have vastly different lifestyle and traditional risk factor profiles, immune deficiency, rather than other risk factors for cancer, is responsible for the increased risk. Infection-related cancers (anal cancer, orophargyneal cancer and hepatocellular carcinoma) will likely become increasingly significant complications of long-term HIV infection.

Anal Cancer

Although anal cancer is uncommon in the general population [32], its incidence has been rising for the last several decades [36]. In the United States, the rates of anal cancer among men who have sex with men (MSM) and immunosuppressed men now exceed the rates of cervical cancer among women [37]. As such, anal cancers have become an important cause of morbidity among HIV-infected persons [5]. In the NA-ACCORD study, HIV-infected MSM experienced the greatest risk for anal cancer with incidence rates greater than 80 times as high as HIV-uninfected individuals. Both HIV-infected men and women had substantially higher rates than HIV-uninfected men and women, and HIV-infected men and women had similar rates [38].

The impact of ART on incidence of anal cancer, however, is somewhat conflicted. Using longitudinal data from the US Military Natural History Study (1985–2005), incidence rates of anal cancer have progressively increased during the HIV epidemic. Crum-Cianflone et al noted that persons with HIV infection for more than 15 years had a 12-fold higher rate of anal cancer than those with less than 5 years [29]. This suggests that the improved survival for HIV-infected individuals in the HAART era results in longer exposure to HPV infection, which may result in increased risk of HPV-associated cancers. However, in a different cohort, the incidence of anal cancer declined during 2004–2007 as compared to 1996–1999 [12]. In another study, rates of anal cancer for HIV-infected individuals increased after the early ART era and then plateaued in more recent years [38]. These conflicting results

perhaps reflect the competing forces of improvement in immune function with HAART leading to better control of co-infections, and underlying immunosuppression [39].

The relationship between CD4 count and anal cancer is also unclear. In multivariate models, it has been demonstrated that a longer exposure to CD4 cell counts < 200 cells/mm3 and between 200–350 cells/mm3 (HR, 1.29; 95% CI, 1.02–1.62) was significantly associated with anal cancer [39,65]. Silverberg et al also found that in the NA-ACCORD study, baseline CD4 < 200 cells/mm was associated with incident anal cancer. However, those with higher CD4 counts also had increasing anal cancer incidence rates between 1996–1999 and 2000–2003 [38]. As HIV-infected persons are experiencing longer life expectancies and HAART does not appear protective of anal cancer, studies on preventive strategies are needed.

Head and Neck Cancers

While the majority of head and neck squamous cell cancers (HNSCC) worldwide are attributable to tobacco and alcohol exposure, oral HPV infection has recently been noted to be an important cause of head and neck cancer [40]. HPV16 accounts for the overwhelming majority (90–95%) of HPV-positive oropharyneal cancers, whereas HPV18, 33, 35, 45, and 59 account for the remainder [41]. Individuals with HIV/AIDS are consistently reported to have a two to four-fold increase in risk for head and neck cancers [42–43]. In a recent meta-analysis, risk of oral cavity and pharynx cancer was two-fold higher among persons with HIV/AIDS [13]. When risk is stratified by anatomic site of the tumor, risk for HPV-related HNSCC (i.e. oropharynx or tonsillar) is consistently elevated from two to six-fold [44].

In the HIV Cancer Match study, risk of oral cavity/pharynx cancer is elevated among HIV-infected individuals with mild-moderate immunosuppression (median CD4 ~500 cells/mL) prior to AIDS diagnosis (SIR 1.7; 95% CI 1.1–2.5]. Incidence rates for oropharyngeal cancer also increased with severity of immunosuppression, as demonstrated by the fact that risk for oropharyngeal cancer is increased for HIV-infected individuals after a diagnosis of AIDS relative to prior to AIDS diagnosis (RR 3.6; 95% CI 1.6–8.2) [3]. However, HAART does not appear to reconstitute HPV-specific immunity, as some reduction in risk for oropharyngeal cancer in the post-HAART era (SIR 0.6; 95% CI 0.3–1.4) has been reported [3] but not consistently [14, 43].

Hepatocellular Carcinoma

Persons infected with HIV, especially injecting drug users (IDU), have a greatly increased incidence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection compared with the general population; therefore, they are at a greater risk for hepatocellular carcinoma (HCC) [13, 45]. Early studies on the natural history of HIV and hepatitis co-infection have shown that HIV-related immunosuppression worsens the risk of cirrhosis and liver-related death [46]. However, in the era of HAART, co-infected patients did not necessarily have higher incidence of HCC when compared to mono-infected patients [47].

HAART, along with better HCV treatments and improved medical management of advanced liver disease, may be associated with a decreased risk of hepatic decompensation and increased survival of co-infected patients with cirrhosis. As a result, the probability of

developing HCC became elevated [48–50]. HIV/HCV-coinfected patients in older studies typically received suboptimal ART, and uncontrolled HIV infection might have shortened the survival of co-infected patients with end-stage liver disease to such an extent that possibly HCC did not have a chance to emerge. In one recent cohort of treated HIV-infected patients with primarily HCV-induced cirrhosis, the incidence of HCC was as high as 6.7 per 1000 patients-years [51].

Both HBV and HCV causes HCC, but the difference in their predominant route of transmission lead to the fact that HIV-infected MSM who developed HCC are more likely to have HBV, whereas HIV-infected IDU with HCC would be more likely to have HCV [27,28]. HIV worsens the clinical outcome of HBV infection by hastening progression to cirrhosis [52] and liver-related death [53], particularly at low CD4 counts [54]. A nested case control study in the Swiss HIV Cohort Study showed that lower CD4 cell counts increased the risk for HCC among persons infected with HIV. The effects of CD4 cell count were predominantly noted in the risk categories of men having sex with men/heterosexual/other, rather than injecting drug users [55]. It has been speculated that the association of HBV with HCC is stronger than that of HCV with HCC. However, the number of HCC cases in this study is small and limited its statistical power. The significance of the dichotomy between HBV-positive HCC arising in MSM and HCV-positive HCC in IDU should be validated in larger cohorts.

Lung cancer

Lung cancer is the most common NADC and leading cause of cancer-related mortality among HIV-infected individuals [56]. Increased rates of lung cancer in HIV-infected patients, compared with uninfected patients, have been demonstrated in multiple prior studies [57–63], but they were variously affected by important limitations. For example, Chaturvedi et al found that the risk for lung cancer was elevated among people with AIDS in the 4–27 months after AIDS diagnosis, and the risk was especially high for those aged under 30 years. However, actual smoking data were not available and observed incidence was compared with general population rates and rates from a lung cancer prediction model for smokers [57]. A retrospective cohort study at a HIV specialty clinic in Baltimore conducted by Engels et al also found increased lung cancer risk even after adjustment for smoking [59]. Unfortunately they did not have an HIV-uninfected cohort for comparison and they used SEER data from Detroit, an urban center similar to Baltimore [59]. Engels et al found that HIV-infected individuals had twice the risk of lung cancer in the AIDS Link to the Intravenous Experience (ALIVE) cohort [61]. However, this study enrolled between 1988 and 2003, when mortality due to AIDS events still dominated clinical outcomes [61]. Finally, Levine et al conducted a prospective study of lung cancer incidence using data from Women’s Interagency HIV Study and demonstrated that HIV infection was strongly associated with smoking behaviors that increased lung cancer risk [62]. Only 14 cases of lung cancer were identified, however, which significantly limited their statistical power [62]. The major confounding factor is that there is a higher prevalence of smoking in HIV-infected patients compared with most of the general US population [63].

HIV was established as an independent risk factor for lung cancer using data from Veterans Aging Cohort Study and Veterans Affairs Central Cancer Registry [64]. The incident rate ratio of lung cancer associated with HIV infection remained significant (IRR 1.7; 95% CI 1.5–1.9) after adjusting for age, sex, race/ethnicity, smoking prevalence, previous bacterial pneumonia, and chronic obstructive pulmonary disease. Lung cancer stage at presentation did not differ between HIV-infected and uninfected patients, indicating that surveillance bias was an unlikely explanation for this finding [65].

The relationship between CD4 cell count, degree of immunosuppression, and subsequent predisposition for lung cancer remains unclear. A large, multicenter cohort study of 20,775 HIV-infected persons showed a trend toward increased incidence of lung cancer in those with CD4 cell count at or below 200 cells/ml (relative risk: 2.2; CI: 1.3–3.6) [65]. However, this study also found that incidence rates of lung cancer were similar between HIV-infected and HIV-negative persons once adjusted for demographic- and infection-related factors. In contrast, a study by Prosperi et al. reported increased incidence of NADCs (including lung cancer) in persons with CD4 cell count of at least 500 cells/ml [66]. Because the absolute risk of developing malignancies at a CD4 cell count >350 cells/ml does not seem to be zero, these findings further support the need to continue to study the potential effect of starting HAART earlier than what is recommended by the present guidelines.

Hodgkin lymphoma

Hodgkin lymphoma (HL) is increased approximately 10-fold in people with HIV [13]. Most HL cases in persons with HIV/AIDS are mixed cellularity and lymphocyte-depleted subtypes, whereas the nodular-sclerosing subtype predominates in young adults without HIV/AIDS [67,68]. It is not surprising that HIV/AIDS-related immunosuppression would affect HL risk and subtype distribution, since persons with genetic conditions associated with T-lymphocyte immune dysfunction have a higher risk of HL, and patients with HL may have underlying abnormalities of T-cell immunity [68].

As a matter of fact, the overall relative risk for development of HL has been found to be elevated in HIV-infected men and women regardless of route of HIV transmission starting from 60 months before AIDS to after the onset of AIDS [69]. Therefore, HL is likely to be genuinely associated with immune dysfunction. However, it is interesting that the incidence of HL has not decreased in the HAART era, and in fact two large studies in the US have reported increasing rates [2–3,5]. Among people with AIDS, rates of HL are highest in people with moderate rather than profound immunodeficiency, and nodular-sclerosing HL is uncommon in those with severe immunodeficiency [70].

The relationship between immunodeficiency, HL development and HL subtypes is unclear. HAART use has improved immunity after AIDS onset, paradoxically increasing HL incidence among persons with HIV/AIDS. The cellular background surrounding H-RS cells may be altered with severe immunosuppression [71–76]. Whether this change affects its categorization as HL or whether it inhibits or delays HL development is unknown. Epstein-Barr virus (EBV) DNA is detectable in high proportions of AIDS-associated HLs [77]. AIDS-associated NHLs are also often EBV-positive [78]. Both HL and NHL appear to

develop from B-lymphocyte transformation [79]. Therefore, EBV-associated subsets of HL may be associated with immune dysfunction through similar mechanisms underlying the association with NHL.

Conclusion

Non–AIDS-defining cancers are a rising health concern among HIV-infected patients. HIV-infected patients are at increased risk for several cancers compared to the general population; anal cancer, hepatocellular carcinoma, Hodgkin lymphoma, and lung cancer all have good evidence demonstrating an enhanced risk in HIV-infected population. However, the higher risk of lung cancer suggests greater impact and need for smoking cessation and should be evaluated further. Prevention efforts in HIV-infected persons should continue to focus on infection-related cancers, including screening for anal dysplasia and the evaluation of more routine vaccinations and antiviral treatment for infections such as hepatitis B. There is currently an AIDS Malignancy Consortium-sponsored clinical trial for HPV vaccine in young HIV-infected men who have sex with men. For anal squamous cell cancer, universal guidelines for screening and detection of early lesions may also greatly benefit this population. The care of patients with HIV will become more complicated as patients grow older, as they develop additional co-morbidities and their treatment becomes more complex due to HIV. Multidisciplinary teams will be needed to confront unique challenges that arise.

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