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COMMENTS AND CONTROVERSIES

Moving Forward in HIV-Associated Cancer

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Cancer has been linked to HIV since the earliest days of the epidemic. The unusually frequent occurrence of Kaposi sarcoma (KS) among men who have sex with men (MSM) in 1981 was a sentinel observation leading to the inclusion of KS in the first AIDS case definition.[1,2] More than three decades later, major research investments have led to striking advances in understanding HIV pathogenesis, with antiretroviral therapy (ART) reducing AIDS complications and allowing HIV-infected individuals to experience life expectancy approaching that of persons without HIV.[3,4]

HIV confers an increased risk for many cancers.[5-9] Although ART has reduced incidence of certain cancers like KS and non-Hodgkin lymphoma (NHL), risks for these cancers are still increased.[5,8,10] With reduced mortality from AIDS in the ART era, HIV-infected people are also aging, leading to a growing cancer burden.[11] As a result, cancer has become a leading cause of HIV-associated death in resource-rich settings, and the leading cause in several HIV cohorts.[12-15] Many uncertainties remain about the underlying pathogenesis of cancer, as well as optimal prevention and treatment strategies in HIV-infected populations. Because HIV-infected individuals on effective ART are increasingly unlikely to die of AIDS, tailored cancer prevention and treatment are needed to maximize life expectancy gains.

Against this background, there is an opportunity to develop a modern, global agenda for HIV-associated cancer which is well suited to the current era. We believe such an agenda requires epidemiologic research that is biologically informed, greater molecular insights to guide treatment, optimized cancer screening and prevention strategies, and inclusion of HIV-infected populations from resource-limited settings.

Biologically Informed Epidemiologic Research

Malignancies associated with HIV have been historically dichotomized as AIDS-defining cancers (ADCs) or non–AIDS-defining cancers (NADCs), according to the 1993 Centers for Disease Control (CDC) definition.[16] This dichotomy groups together KS, certain NHL subtypes, and cervical cancer as ADCs, while classifying all other cancers as NADCs despite clear epidemiologic and biologic links to HIV in many instances. More recently, malignancies in HIV-infected people have been categorized as infection-related or infection-unrelated.[7] Grouping cancers in these ways can increase the number of cancers under evaluation in research studies.

However, when substantial etiologic heterogeneity exists within cancer groups defined for analytic purposes, these groupings can obscure rather than facilitate pathogenic and clinical insights. Table 1, which lists several cancers for which risk is increased in the context of HIV, demonstrates that similarities and differences between cancers often cut across conventional classification schemes. Although the ADC/NADC and infection-related/infection-unrelated distinctions have questionable relevance, they remain in widespread use, and many HIV cohorts continue to collect data solely on ADCs.

To demonstrate, cervical cancer is an ADC, and anal cancer is an NADC. However, among HIV-infected people in the United States, excess risk is greater for anal cancer than for cervical cancer.[5-8,17,27] This pattern may, in part, be a result of a high proportion of MSM in the US HIV-infected population,[28] as well as successful cervical cancer screening among HIV-infected women.[29] Both cancers progress through defined precursor lesions and are almost always caused by human papillomavirus (HPV).[18,19] Both cancers are preventable by screening and vaccination and are treated similarly with surgery and/or chemoradiotherapy. In this instance, the ADC/NADC distinction obscures the close kinship of these two cancers. Similarly, assignment of NHL and Hodgkin lymphoma to different categories by using the ADC/NADC scheme may be problematic, ignoring similarities across these lymphomas with respect to Epstein-Barr virus (EBV), which is etiologically implicated in a large portion of cases in HIV-infected people.[20-23] These shortcomings highlight the fact that the 1993 AIDS case definition was developed as a surveillance tool to track the epidemic and that the ADC/NADC distinction has major limitations as a cancer classification scheme.

Grouping cancers as infection-related or infection-unrelated is another strategy in epidemiologic research. However, for some cancers, only subsets of cases are caused by infection. Classifying cancers such as NHL or head and neck squamous cell carcinoma (HNSCC) as infection-related, without pathologic or molecular identification of oncogenic viruses in tumor specimens (EBV for NHL, HPV for HNSCC), invariably misclassifies many virus-negative tumors.[20,24,25] EBV is present in only 40% to 60% of NHL specimens, although there is marked variation across histologic subtypes.[20,21] For HNSCC, increased rates of oral HPV acquisition or persistence may contribute to the two- to three-fold increase in HNSCC associated with HIV,[5-8,17] although the relative contribution of HPV versus tobacco and alcohol use remains largely unknown in the HIV-infected population.

Table 1. Classification and Features of Selected HIV-Associated Cancers

Cancer Type	Known Oncogenic Virus	Prevalence in HIV-Associated Tumors (%)	Category	Infection Related/ Infection Unrelated	Relative Risk Compared With General Population	Currently Amenable to Screening	Currently Vaccine Preventable
Cervix	HPV	100	ADC	Related	3-15	Yes	Yes
Anus	HPV	> 90	NADC	Related	10-100	Yes	Yes
Head and neck	HPV	Unknown for HIV-infected persons; up to 70 for oropharynx cancers in HIV-uninfected persons	NADC	Related	1.5-3	No	No
Lung	None		NADC	Unrelated	2-4	Yes	No
Melanoma	None		NADC	Unrelated	2-3	Yes	No
Liver	HBV/HCV	> 90	NADC	Related	3-10	Yes	Yes (HBV)
Kaposi's sarcoma	KSHV	100	ADC	Related	100-1,000	No	No
Multicentric Castleman disease*	KSHV	100	—	Related	—	No	No
Non-Hodgkin lymphoma (all)	EBV/KSHV		ADC	Related	5-50	No	No
Primary effusion lymphoma	EBV/KSHV	50-80/100	ADC	Related	—	No	No
Primary CNS lymphoma	EBV	100	ADC	Related	100-200	No	No
Diffuse large B-cell lymphoma	EBV	40-60	ADC	Related	5-20	No	No
Burkitt's lymphoma	EBV	30-50	ADC	Related	20-100	No	No
Hodgkin lymphoma (all)	EBV	> 80	NADC	Related	5-20	No	No
Nodular sclerosis	EBV	20-30	NADC	Related	—	No	No
Mixed cellularity	EBV	> 90	NADC	Related	—	No	No
Lymphocyte depleted	EBV	> 90	NADC	Related	—	No	No

NOTE. Data on relative risks and the proportions of tumors associated with oncogenic viruses derive from Patel et al,[5] Engels et al,[8] Shiels et al,[10] Chaturvedi et al,[17] Walboomer et al,[18] De Vuyst et al,[19] Dunleavy et al,[20] Swerdlow et al,[21] Glaser et al,[22] Tirelli et al,[23] Gillison et al,[24] Chaturvedi et al,[25] and Brau et al.[26]

Abbreviations: ADC, AIDS-defining cancer; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; KSHV, Kaposi's sarcoma–associated herpesvirus; NADC, non–AIDS-defining cancer.

*Multicentric Castleman disease is an aggressive lymphoproliferative disorder, although it is not considered a malignant neoplasm.

Moreover, different oncogenic viruses cause cancer by different mechanisms. Some viruses (eg, EBV for NHL) cause cancer by directly transforming infected cells. In contrast, chronic hepatitis B and C infections are associated with increased risk of NHL through indirect mechanisms that likely involve chronic immune activation and B-cell stimulation.[30-32] Although EBV plays an important role in NHL occurrence among HIV-infected individuals, hepatitis B and C infections do not appear to contribute.[33,34] Grouping together infections or infection-related cancers may therefore lead to uninformative results in epidemiologic studies and obscure relevant biologic mechanisms.

Molecular Insights to Guide Treatment

Cancer research has entered a molecular age, and characterizing tumors with respect to causation by oncogenic viruses, as well as immunophenotypic and genomic features, is increasingly important to optimize treatment. For example, treatment de-escalation is under active investigation in HPV-associated HNSCC, given the overall better prognosis for these tumors.[35,36] Likewise, sorafenib may be a more effective treatment for hepatocellular carcinoma caused by hepatitis C than hepatitis B for reasons that have not been fully elucidated.[37-39] Different treatment approaches may soon be considered for diffuse large B-cell lymphoma subtypes defined by gene expression profiling,[40,41] although clinical trials for HIV-associated lymphoma have often enrolled patients with diffuse large B-cell lymphoma or Burkitt lymphoma together and treated them as a single clinical entity. Genomic characterizations have been infrequently applied to HIV-infected patients for whom tumor biology may differ from that of noninfected patients.[42-45] Tumor biology also may differ within HIV-infected populations on the basis of when cancer occurs along the clinical course of HIV infection, given complex interactions between ART use, HIV replication, immune suppression, aging, and other risk factors that are dynamic over time.

Given the rarity of HIV-associated cancer in resource-rich settings, no single center will have enough cases to study individual cancers, especially molecularly defined subtypes. However, more granular characterizations of tumors in HIV-infected patients can be undertaken by pooling records and specimens from existing HIV consortia. Such studies may be small and have limited power but can provide opportunities to explore molecular cancer subtypes in detail among HIV-infected persons. Research on HIV-associated cancers can also be better integrated into the larger cancer research agenda, with extrapolation when appropriate from studies in noninfected patients. In the modern ART era, it should also be possible to include HIV-infected patients as a subgroup in large collaborative studies,[46] as is now being done for Hodgkin lymphoma.[47]

Examples of these efforts are ongoing in the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) and cooperative clinical trial groups supported by the National Cancer Institute (NCI), such as the AIDS Malignancy Consortium (AMC).[48] In CNICS, a standardized data collection process for cancer has been implemented that allows for a growing body of research that addresses HIV-associated cancer.[49-52] CNICS has also launched efforts to pool specimens to perform translational studies of HPV in HIV-associated HNSCCs and molecular profiling of lymphomas before and after ART.

Optimized Cancer Screening and Prevention

In HIV clinical settings, cancer screening is typically based on guidelines developed for the general population, like those endorsed by the United States Preventive Services Task Force (USPSTF). With normalizing life expectancy, this may be appropriate for cancers for which risk is similar between HIV-infected and HIV-uninfected people, such as breast and prostate cancer. However, for other cancers, performance of screening interventions may be sufficiently different in HIV-infected individuals to warrant modified approaches.

For instance, cervical cancer screening intervals may need to be shorter in HIV-infected women because of more frequent acquisition of and persistence of oncogenic HPV subtypes and higher risk of progression for precancerous lesions.[53,54] Likewise, performance of low-dose computed tomography (LDCT) for lung cancer screening may be different in HIV-infected smokers who have high rates of lung cancer but are also more likely to have LDCT-detected radiographic abnormalities that require additional diagnostic work-up.[55,56]

In addition, cancer screening interventions without evidence of benefit in the general population may be of value in HIV-infected individuals because of different cancer risk profiles. One example is screening for anal cancer, which has been widely adopted in HIV clinics to reduce the high rates of anal cancer observed especially among HIV-infected MSM. Current adoption is largely based on extrapolation from cervical cancer screening, and rigorous evaluation specifically for anal cancer screening is ongoing.[55] In addition, the optimal application of cancer screening in HIV-infected individuals might vary with time on ART, since risk for various cancers is not uniformly distributed over time.[51]

Vaccine strategies are also generally similar between HIV-infected and HIV-uninfected populations, as in current recommendations for HPV vaccination among children and young adults. However, potential differences in HPV subtypes, age at acquisition, and vaccine responsiveness may call for more nuanced guidelines specifically for HIV-infected individuals.[57] These issues may be particularly salient in resource-limited settings in which introduction of HPV vaccine has only recently begun in many countries, and where scarce resources call for cost-efficient vaccine programs with optimal targeting of at-risk populations. Cancers caused by EBV and Kaposi's sarcoma-associated herpesvirus may eventually also be preventable with vaccines, with early candidate vaccines for EBV showing promise.[58,59]

Inclusion of HIV-Infected Populations From Resource-Limited Settings

The paucity of research related to HIV-associated cancer in sub-Saharan Africa provides a strong incentive to extend modern cancer care and research to settings where resources are severely constrained to learn lessons that are applicable at a global level.[60] Of 34 million HIV-infected individuals worldwide, 24 million (69%) reside in sub-Saharan Africa.[61] There is now the possibility of developing HIV-associated cancer research programs in countries where large numbers of patients can provide data that are informative to both resource-limited and resource-rich settings. Such collaborations can provide a platform for studying HIV-associated cancers that occur frequently in many parts of Africa (eg, conjunctival squamous cell carcinoma) but rarely in other parts of the world. Cancer control among HIV-infected people in sub-Saharan Africa is handicapped by a high prevalence of oncogenic viruses,[62] advanced HIV illness before ART initiation, and

limited ART availability, although remarkable progress has been made and many countries now surpass the United States in ART coverage rates.[61] Such progress has led to an HIV epidemic in evolution, which increasingly resembles resource-rich settings with high burdens of chronic disease and cancer in aging HIV-infected populations. Cancer screening is scarce in sub-Saharan Africa, although the HIV epidemic has been a major impetus for introducing cervical cancer screening.[63,64] Ongoing African studies of the AMC and the International Epidemiologic Databases to Evaluate AIDS (IeDEA) consortium represent a promising foundation on which to build robust cancer research collaborations in this part of the world.

In conclusion, a global, forward-looking agenda for HIV-associated cancer should now be possible just as it has been for HIV, and modern frameworks should replace outdated ones. The ADC/NADC distinction predates the modern ART era and has little scientific relevance. This construct should be abandoned in epidemiologic research addressing HIV-associated cancers. Instead, research efforts should be focused on individual cancers or, when necessary for analytic purposes, grouping cancers into categories that are informed by underlying biologic mechanisms. In clinical treatment studies, molecular tools should be used to identify clinically relevant patient subsets, as is routinely done for HIV-uninfected patients. Optimizing cancer screening and prevention strategies for HIV-infected populations is equally important. Finally, extending care and research for HIV-associated malignancies to parts of the world most affected by these diseases can lead to important scientific and humanitarian advances. Together, these efforts will allow patients to fully reap the benefits of modern ART wherever they may live.

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