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Non-AIDS-defining malignancies in HIV-infected persons: etiologic puzzles, epidemiologic perils, prevention opportunities

E.A. Engels

Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD

Abstract

Non-AIDS-defining malignancies have come to represent a growing fraction of the overall cancer burden in HIV-infected people, as improvements in HIV therapy prolong survival and reduce the incidence of AIDS-associated cancers. This review focuses on five non-AIDS-defining malignancies for which HIV-infected persons have an elevated risk, for which risk is substantial or increasing over time, and for which HIV infection may play an etiologic role. Among HIV-infected persons, lung cancer risk is high, in part due to frequent tobacco use in this population. Risks of anal cancer and liver cancer are also elevated, related to the high prevalence of infections with human papillomavirus and hepatitis B and C viruses. In addition, risk is elevated for Hodgkin lymphoma and several rare skin cancers, including Merkel cell carcinoma and sebaceous carcinoma. For anal cancer and Hodgkin lymphoma, it is particularly concerning that incidence in HIV-infected persons has risen in recent years, when highly active antiretroviral therapy has been available. Accumulating evidence supports the possibility that the high prevalence of known carcinogenic exposures (e.g., tobacco) and infections with oncogenic viruses does not completely explain the occurrence of these cancers. Indeed, HIV may act to increase the risk for each of these five non-AIDS-defining malignancies, although the mechanisms may vary, including immunosuppression, immune reconstitution, and chronic inflammation. These non-AIDS-defining cancers also present important opportunities for prevention (e.g., smoking cessation), screening (e.g., periodic anal Pap smear screening), and early detection.

Introduction

Since the beginning of the HIV epidemic, cancer has figured prominently in the spectrum of immunodeficiency-related manifestations. In particular, the risk of Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL) is vastly higher among HIV-infected persons than in healthy persons (e.g., standardized incidence ratios [SIRs] of 20,000-50,000 and 50-80, respectively, comparing risk among people with AIDS in the U.S. to risk in the general population) (1). Cervical cancer risk is also elevated among HIV-infected women, although to a lesser degree (i.e., SIRs 4-8) (1). These three malignancies are considered AIDS-defining conditions by the U.S. Centers for Disease Control and Prevention (2). All three are caused by oncogenic viruses: human herpesvirus 8 for KS; Epstein Barr virus (EBV) for the two most common AIDS-associated NHL subtypes, diffuse large B cell NHL and central nervous system NHL; and human papillomavirus (HPV) for cervical cancer (3,4).

A major feature of these cancers in HIV-infected persons is their association with immunosuppression. For KS and EBV-related NHL subtypes, risk increases as the CD4 count declines (5). This association with CD4 count has not been apparent for cervical cancer (5), although HIV-infected women with low CD4 counts have an elevated risk of persistent HPV infection and progression to pre-cancerous cervical lesions, compared to women with higher CD4 counts (6). Risk of all three AIDS-defining malignancies is also elevated among solid organ transplant recipients, another immunosuppressed population (7).

In developed countries, the availability of highly active antiretroviral therapy (HAART) beginning in 1996 has led to improvements in immunity and declining AIDS-related morbidity and mortality (8-10). HAART substantially reduces risk of KS and EBV-related NHL (11-13). For unknown reasons, KS and NHL incidence rates were falling even during the 1980s and early 1990s among people with AIDS in the U.S., but introduction of HAART in 1996 led to a further drop (Figure 1) (1). As a result of these declines, non-AIDS-defining malignancies now represent a much larger fraction of the overall cancer burden in people with AIDS compared with the pre-HAART era (Figure 1) (1). Among less immunocompromised individuals HIV-infected persons, non-AIDS-defining cancers now comprise the majority of all incident cancers (e.g., in the U.S.: 58% of all cancers, vs. 31% in the pre-HAART era) (14).

This review considers the epidemiology of several major non-AIDS-defining cancers in HIV-infected persons. The focus is on malignancies for which HIV-infected persons have an elevated risk, for which risk is substantial or may increase over time, and for which HIV infection may play an etiologic role in the development of the cancer. The review does not focus on common cancers for which risk is not elevated in HIV-infected persons compared with the general population, or where evidence for an increase is inconclusive (e.g., colon cancer) (15), although these cancers represent an important cause of morbidity. Most attention will be directed at cancer in developed countries in the West, because it is these countries where HAART has been most widely available and for which most epidemiologic data exist.

Non-AIDS-defining malignancies: epidemiologic pieces of the etiologic puzzle

Clinicians caring for HIV-infected people increasingly recognize a diverse group of non-AIDS-defining cancers as important sources of morbidity and mortality. Many of these malignancies are due to chronic infections with oncogenic viruses (e.g., liver cancer related to chronic hepatitis C and B viruses [HCV and HBV], anogenital cancers related to HPV). Others arise from tobacco (e.g., cancers of the lung, head and neck, bladder) and alcohol abuse (e.g., cancers of liver and head and neck), which are common problems in HIV-infected populations in North America and Europe.

Five of these non-AIDS-defining cancers deserve special attention and will be highlighted in this review (Table 1). These malignancies (lung cancer, Hodgkin lymphoma, anal cancer, liver cancer, and non-melanoma skin cancers) are among the most common among HIV-infected persons, and each arises at increased frequency compared with the general population (7). As will be described, a concerning aspect of the epidemiology is that for two of the malignancies (Hodgkin lymphoma and anal cancer), incidence among HIV-infected persons has been increasing in the HAART era.

As reviewed below, the epidemiologic data suggest that HIV may facilitate, at least indirectly, the development of these non-AIDS-defining cancers. For Hodgkin lymphoma, HIV-infected persons present more frequently with extranodal disease and at an advanced stage than HIV-uninfected individuals (16). In contrast, data are lacking for carcinomas on whether the

phenotype (e.g., histologic subtype, molecular tumor characteristics, or potential to metastasize) differs in any essential way from the phenotype of tumors in uninfected individuals. For lung cancer and liver cancer, HIV-infected individuals tend to present at a more advanced stage than uninfected individuals (17-20), but this difference could be secondary to poor access to medical care and delayed diagnosis. Likewise, lung cancers in HIV-infected individuals manifest greater genetic instability than those from uninfected persons (21), but this characteristic could merely reflect the advanced stage of the tumors. Prognosis among HIV-infected cancer patients is typically worse than in uninfected cancer patients (17,20,22), which plausibly could reflect advanced stage of cancer diagnosis, differences in cancer treatment, and AIDS-related mortality. One intriguing exception where HIV infection may alter the phenotype is non-melanoma skin cancer. Immunosuppressed solid organ transplant recipients have a greatly elevated risk for developing multiple, highly aggressive squamous cell skin cancers (23), and similar cases have been described in HIV-infected persons (24,25).

A reasonable working hypothesis is therefore that non-AIDS-defining malignancies in HIV-infected persons are not pathologically distinct entities. Rather, these tumors represent the same cancers as seen in uninfected individuals, but they occur at an increased rate among HIV-infected persons. This increased incidence could, in turn, reflect a high prevalence of known cancer risk factors, an independent effect of HIV on progression to cancer, or a biological interaction of HIV with the known risk factors. The following sections review the epidemiologic data and consider some potential biological mechanisms whereby HIV might facilitate development of these malignancies.

Lung cancer

Lung cancer is the most common non-AIDS-defining malignancy among HIV-infected individuals in developed countries (7). Risk is elevated for all major lung cancer subtypes (adenocarcinoma, squamous cell carcinoma, and small cell carcinoma) (18,26). The high risk of lung cancer partly relates to a high prevalence (40-70%) of tobacco use among HIV-infected individuals (27-29), and almost all lung cancer cases occur in smokers (11,26,30). However, lung cancer risk is also increased in immunosuppressed transplant recipients (7), a group in which smoking is not especially common. Furthermore, recent studies suggest that the elevated risk among HIV-infected persons cannot be entirely explained by their frequent tobacco use (18,26,31). These studies have limitations, because it has been challenging to obtain detailed smoking data from a large enough HIV-infected population to reliably estimate cancer risk. Nonetheless, under plausible assumptions the recent analyses suggest that lung cancer risk is 3-4 times higher in HIV-infected persons than in uninfected persons after adjustment for smoking intensity and duration (18,26,31).

Lung cancer can develop at any point in the course of HIV disease, although risk increases somewhat in the periods immediately before AIDS and subsequent to an AIDS diagnosis (18). Lung cancer risk is not closely related to CD4 count or HIV viral load (18,26,31). Data on whether HAART use is associated with a decrease in lung cancer risk are conflicting (11, 15,26,31), but lung cancer incidence has not declined noticeably in recent years as HAART has become widely available and increasingly used (15,18,26,31).

Hodgkin lymphoma

Hodgkin lymphoma risk is substantially elevated among immunosuppressed HIV-infected persons and transplant recipients (7,32). Most Hodgkin lymphoma cases are of the mixed cellularity subtype (16,32,33), in distinction to a predominance of nodular sclerosis subtype seen in young adults in the general population. In Hodgkin lymphoma, the malignant cell is the Hodgkin Reed-Sternberg cell, a transformed B lymphocyte that comprises only a small

minority of the tumor cell population; the remainder of lesional cells constitute a population of non-malignant immune and stromal cells supported by cytokines and other cell signals from the Hodgkin Reed-Sternberg cell (34,35). In immunocompromised persons, Hodgkin Reed-Sternberg cells are almost always EBV positive (16,36), suggesting that the increased risk of Hodgkin lymphoma in HIV-infected persons is due to loss of control of EBV infection. In accord with a model in which loss of immune control of latent EBV infection leads to Hodgkin lymphoma, Hodgkin lymphoma risk among HIV-infected persons rises following an AIDS diagnosis (37).

Nonetheless, the relationship between immunosuppression and development of Hodgkin lymphoma is complex. Paradoxically, in light of the likely involvement of EBV, Hodgkin lymphoma risk increased during the 1990s among HIV-infected persons (Figure 2, panel A) (1,14,15,38), during a period when HIV therapy became increasingly effective and should have led to improved immune control of EBV infection. It is likewise surprising that Hodgkin lymphoma risk in persons receiving HAART appears similar to or higher than risk in HIV-infected persons not on HAART (11,33). Additionally, among HIV-infected persons, the association between CD4 count and Hodgkin lymphoma risk has a non-linear “inverted U” shape (Figure 2, panel B) (32). Specifically, Hodgkin lymphoma risk increases with a decline in CD4 count to 225-249 cells/mm³ but then falls again as the CD4 count declines further.

Anal cancer

Anal cancer is caused by persistent infection with oncogenic subtypes of HPV (39). Anal cancer incidence is especially high in HIV-infected men-who-have-sex-with men (40), due to sexual transmission of HPV through anal intercourse. In this group, anal HPV infection is almost universal, chronic, and frequently characterized by the presence of multiple HPV subtypes (41,42). Anal cancer incidence is also elevated among other HIV-infected men and women (40), which could partly reflect acquisition of HPV through anal sex, but also probably reflects indirect transmission of HPV related to other sexual acts (i.e., transfer of HPV from genital sites) (43).

The role of HIV-related immunosuppression in promoting development of anal cancer has been somewhat difficult to establish. With HIV, detection of anal HPV increases with declining CD4 count (44), likely as a result of decreasing clearance of HPV with immunosuppression. Likewise, the risk for anal cancer precursor lesions (i.e., anal intraepithelial neoplasia) rises with decreasing CD4 count among HIV-infected individuals (41,43,44). Further pointing to the importance of HIV-induced immunosuppression, recent research indicates that the incidence of anal cancer is inversely related to CD4 count and increases following an AIDS diagnosis (45,46), although these associations were not seen in the pre-HAART era (40). Anal cancer incidence is also elevated among solid organ transplant recipients (7). Finally, chronic inflammation may also be important in promoting the development of anal cancer (47), although the effects of HIV on modulating this process are unknown.

Given these findings implicating immunosuppression, one might have predicted a decline in anal cancer incidence with introduction of HAART in 1996. However, a number of epidemiologic studies have found either a stable or increasing occurrence of anal cancer since the advent of HAART (1,15,45,46,48). Data are conflicting with regard to the prevalence, persistence, and regression of anal intraepithelial neoplasia in relation to HAART use (49). Perhaps most surprising, anal cancer incidence actually appears higher in persons who use HAART compared to HIV-infected individuals not receiving HAART (11,45,48).

Liver cancer

In HIV-infected persons, an excess risk of liver cancer (specifically hepatocellular carcinoma) is largely attributable to frequent co-infection with HCV (e.g., in the U.S., 70-95% prevalence among HIV-infected individuals with blood exposures, such as injection drug users and people with hemophilia) and HBV (5-15% prevalence across HIV risk groups in the U.S.) (50). Most HIV-infected liver cancer patients are chronically co-infected with one of these two viruses (19,20,51). Cirrhosis is often present at the time of liver cancer diagnosis (52).

Of interest, the excess risk for liver cancer associated with HCV is more modest among HIV-infected persons than observed in HIV-uninfected persons (i.e., relative risks 2-7 vs. approximately 12) (51,53-55). This apparent difference in risk conveyed by HCV coinfection could reflect a shorter duration of HCV infection among HIV-infected persons than in the general population, or the effects of HIV in driving progression to end-stage liver disease, which could lead to additional mortality that might mask an increased risk of liver cancer (19,20,51,53,56,57). Among HBV-infected persons, liver cancer risk increases with rising HBV replication (58), so risk would be expected to be high among immunodeficient HIV-infected individuals who fail to control HBV (59).

Nonetheless, the effect of HIV infection itself on liver cancer risk has been somewhat uncertain. One study of U.S. military veterans found no difference in liver cancer risk between HCV-infected and HCV-HIV-coinfected individuals (60), suggesting that HIV-related immunosuppression does not play an important role. In contrast, a recent study demonstrated an increase in liver cancer risk among HIV-infected persons associated with declining CD4 count, particularly for HBV-related liver cancer (51). Although some antiretroviral medications can manifest liver toxicity, limited data suggest that HAART use may decrease liver cancer risk (51,61), perhaps due to improved immune control of viral hepatitis.

Finally, although alcohol abuse is prevalent among HIV-infected persons, its effect on liver cancer risk has not been measured. A history of alcohol abuse is less common among HIV-infected liver cancer cases than among uninfected cases (19,52), suggesting that alcohol abuse may have a modest effect on risk.

Non-melanoma skin cancers

Non-melanoma skin cancers are a heterogeneous group of malignancies (62). Chronic exposure to solar ultraviolet light is the major risk factor for all skin cancer subtypes, and their incidence is much greater in non-Hispanic whites (who lack protective skin pigmentation) than other racial/ethnic groups (63,64). Basal cell and squamous cell carcinomas are the most common skin cancer subtypes in the general population and are typically associated with a good prognosis following local excision (64). Unfortunately, most cancer registries do not record the occurrence of these two skin cancer subtypes, which has complicated epidemiologic research.

Despite limitations in available epidemiologic data, it is apparent that immunosuppressed transplant recipients have an elevated risk of basal cell and, especially, squamous cell skin cancers (23,65). Limited data for HIV-infected individuals also show an elevated risk of squamous cell and basal cell skin carcinomas (66), perhaps rising over time (67). Additionally, published case series describe the occurrence in HIV-infected persons (as in transplant recipients) of unusually aggressive squamous cell skin cancers (24,25,68,69). To a lesser extent, melanoma risk also appears increased in HIV-infected persons and transplant recipients (7,15,70), which could relate to immunosuppression but may instead be artifactual (e.g., resulting from heightened medical surveillance).

Notably, HIV-infected individuals and transplant recipients have a markedly elevated risk for two rare subtypes of non-melanoma skin cancer, Merkel cell carcinoma and sebaceous carcinoma (standardized incidence ratios 11 and 8, respectively, among people with AIDS) (70). A novel polyomavirus was recently identified in Merkel cell carcinoma tumors (71).

Of final interest, the occurrence of the various subtypes of non-melanoma skin cancers in HIV-infected persons is largely limited to non-Hispanic whites (25,69,70). Similarly, it is striking that in a follow-up study of kidney transplant recipients in South Africa (72), only whites developed non-melanoma skin cancers, despite the fact that the majority of recipients were non-white; most of the diagnosed skin cancers were squamous cell or basal cell carcinomas, although one case was an appendageal carcinoma. These observations highlight the continued importance of sun exposure even in the setting of immunosuppression.

It may be debated whether non-melanoma skin cancers deserve the same consideration as the other non-AIDS-defining malignancies evaluated in this review. Data are limited regarding risk for the most common non-melanoma skin cancer subtypes (squamous and basal cell carcinomas), while other subtypes potentially linked to oncogenic viruses (e.g., Merkel cell carcinoma and perhaps sebaceous carcinoma) are quite rare. Nonetheless, the available data for HIV-infected individuals and the clear excess risk in solid organ transplant recipients suggest that these cancers may be an under-recognized source of morbidity, especially in non-Hispanic whites.

Immunologic mechanisms: possible new paradigms for HIV-related carcinogenesis

The importance of the established risk factors for these five non-AIDS-defining malignancies (e.g., tobacco, HPV, sunlight; Table 1) cannot be denied. Furthermore, it seems unlikely that HIV-infected persons who lack these exposures are at substantial risk for the cancers. Nonetheless, it would be inappropriate to conclude that HIV is unimportant in the etiology of these non-AIDS-defining malignancies. This situation is similar to that for AIDS-defining conditions, where the presence of additional agents is required for their development. Rather, the relevant question is: in the presence of certain known carcinogens, does HIV infection amplify the effects of these carcinogens to promote development of cancer? The most obvious mechanism by which HIV could facilitate the development of these malignancies is by disturbing the host immune system. Consideration of the epidemiologic evidence and other recent data presented above suggests that several immunologic mechanisms could be involved in the etiology of these malignancies (Table 2).

The simplest immunologic mechanism to consider is HIV-induced depletion of CD4 cells, leading to deficient cell-mediated immunity. This mechanism is highly relevant for KS and NHL (5). The epidemiologic hallmarks of this mechanism are strongly increased risk of cancer compared to the general population and clearcut associations with markers of immunosuppression, such as CD4 count, time relative to AIDS onset, and the protective effects of HAART. Another hallmark is an elevated risk for the cancer among transplant recipients, who receive chronic immunosuppressive therapy to prevent graft rejection. It has been hypothesized that an intact immune system can control or eliminate early cancer precursor cells, protecting against a wide range of cancers (i.e., the immune surveillance hypothesis (73)). Nonetheless, evidence in HIV-infected persons and transplant recipients is strongest that immunodeficiency predisposes to the subset of malignancies caused by oncogenic viruses, likely because of loss of immune control of viral replication and transformation. Regarding the non-AIDS-defining cancers highlighted in this review, this mechanism may be most relevant for some non-melanoma skin cancers, particularly the rare subtypes such as Merkel cell carcinoma and sebaceous carcinoma, where oncogenic viruses could have a direct transforming

role. Although limited data on these skin cancers preclude a definitive assessment, the substantially increased risk compared to the general population, in the absence of another obvious explanation, suggests that HIV-related immunosuppression is relevant.

It is useful to speculate on additional immunologic mechanisms related to HIV infection that could potentially play a role in the development of other non-AIDS-defining malignancies (Table 2). For anal cancer, there are several salient observations: first, low CD4 counts are associated strongly with detection of anal HPV infection and pre-cancerous lesions, but less strongly with risk of anal cancer itself; second, anal cancer risk increases with progressive time relative to an initial AIDS diagnosis; and third, anal cancer incidence has increased during the HAART era and is elevated among individual HAART users. A model that could account for these observations is that HIV-related immunosuppression is relevant at the earliest stages of anal carcinogenesis (such as HPV persistence and development of low-grade squamous intraepithelial neoplasia) but not involved in the later progression to invasive cancer (39). Under such a model, HAART would not result in a benefit if administered after the early steps in this process. Indeed, due to the survival benefits associated with HAART use, persons receiving HAART would live long enough to develop anal cancer. In other words, HAART use increases time spent living with early-stage neoplastic lesions, allowing their progression to invasive cancer. Likewise, the increase in anal cancer risk associated with AIDS onset may not reflect the effects of progressive immunosuppression but rather prolonged time spent living with immunosuppression and duration of HPV-related disease.

Given the rarity of liver cancer, a challenge has been to gather sufficient data to assess the effects of HIV infection and related immunosuppression. One possibility is that deficiency of cell-mediated immunity plays a role in the development of liver cancer by reducing immune control of chronic HCV and HBV infections. However, the situation may be more complicated than for anal cancer. Specifically, for liver cancer, immunosuppression not only predisposes to AIDS-related mortality but also liver-related mortality (56,57,74). In the pre-HAART era, one or both of these competing causes of mortality may have obscured an association between immunosuppression and liver cancer risk.

The elevated risk of lung cancer in HIV-infected smokers probably has a different explanation, since risk is not strongly related to markers of HIV-related immunosuppression such as CD4 count and prior AIDS onset. Also, risk is elevated for all lung cancer subtypes, pointing away from involvement of a single oncogenic virus (and thus, pointing away from immunosuppression). One possibility is that HIV infection promotes the development of lung cancer by causing chronic pulmonary inflammation and repeated lung infections, which could induce DNA damage in a synergistic manner with tobacco (75). In the general population, chronic lung infections due to *Chlamydia pneumoniae* and tuberculosis are linked with an increased risk of developing lung cancer (75). At all stages of infection, HIV is associated with chronic or repeated lung infections, due to micro-organisms that frequently cause pneumonia in the general population (e.g. *S. pneumoniae*) as well as opportunistic micro-organisms (e.g., *Mycobacterium avium intracellulare*, *Pneumocystis jirovecii*). HIV infection also leads to expansion of the pool of pulmonary macrophages and elevated levels in the lung of pro-inflammatory cytokines, such as interleukin 1 beta, tumor necrosis factor, and interferon gamma (76). If HIV amplifies the effects of tobacco by inducing chronic lung inflammation or causing repeated pulmonary insults due to infections, processes that occur at all levels of HIV-related immunosuppression, a strong association of lung cancer risk with CD4 count or advanced HIV disease might not be expected.

For Hodgkin lymphoma, an additional possibility is that some cases arise as part of an immune reconstitution syndrome (32). This hypothesis is consistent with the nonlinear relationship between CD4 count and Hodgkin lymphoma risk, and with rising Hodgkin lymphoma

incidence during the HAART era. Specifically, the increase in CD4 count associated with HAART use among extremely immunodeficient individuals may shift them to a level of immunosuppression (i.e., a CD4 count 200-250 cells/mm³, Figure 2) that puts them at greatest risk for Hodgkin lymphoma. In that setting, Hodgkin lymphoma may develop because the malignant Hodgkin Reed-Sternberg cell may already be present, and partial restoration of immunity allows recruitment of surrounding immune cells and manifestation of the tumor (32). In other cases, Hodgkin lymphoma may develop in a more direct manner with progressive or prolonged immunosuppression. The situation may be analogous to what is observed for KS, another malignancy in which a substantial component of the lesional cells are not actually malignant. While KS most often arises with progressive loss of cell-mediated immunity, cases with onset or worsening related to HAART-induced immune reconstitution are described (77-79).

In the HAART era, several mechanisms in Table 2 are likely to become increasingly important in the development of cancer. The role of these various mechanisms in the etiology of non-AIDS-defining cancers should be evaluated in large, well-designed epidemiologic studies. Ideally, the studies should include detailed data on validated cancer cases, and extensive longitudinal measurements of CD4 count, HIV viral load, and use of antiretroviral medications. Given the rarity of most cancer outcomes, use of pooled data from consortia may be required, and given the complexity of the analyses, replication will likely be necessary.

Finally, it will be important to evaluate the possibility that HIV medications could themselves increase risk for some cancers. A possibility is that some medications may have direct genotoxic effects that initiate or promote development of cancer. For example, zidovudine, a nucleoside reverse transcriptase inhibitor, is incorporated into host DNA and can induce point mutations and chromosomal breaks (80), but whether these changes translate into an increased cancer risk is unknown. Because patients frequently switch antiretroviral medications, and because effects on cancer risk may require years of exposure and follow-up to manifest, it will be extremely challenging to identify whether specific antiretroviral medications cause specific types of cancer.

Prevention, screening, and early detection

Consideration of these non-AIDS-defining cancers highlights clinical and public health opportunities (Table 3). Some potential interventions are straightforward extensions of practices for HIV-uninfected persons and would appear to promise substantial reductions in cancer-related morbidity and mortality. However, their utility and cost-effectiveness for HIV-infected individuals are largely unknown. Detailed evaluation of available, and in some instances, improved strategies will be important before they can be adopted as routine practice.

Counseling by clinicians will play a role in prevention programs. The cornerstone of prevention for lung cancer is tobacco cessation, and given the role of tobacco in other illnesses, programs to encourage HIV-infected individuals to quit smoking should be a priority. Although counseling and available pharmacotherapy are helpful (81), development of more effective interventions in smoking cessation, including those targeted specifically at HIV-infected persons, will be important. Encouraging HIV-infected people to limit the number of their sexual partners may reduce their risk of acquiring new HBV and HPV infections, but condom use is of unproven benefit (e.g., for anal HPV (82)). For individuals with liver disease, abstinence from alcohol may help prevent progression to liver cancer. Finally, encouraging HIV-infected persons to minimize unnecessary sun exposure is prudent to reduce skin cancer risk.

Vaccination strategies may also help prevent cancers. HBV vaccination prevents HBV infection and is associated with reduced occurrence of liver cancer (83). HBV vaccine is less immunogenic among HIV-infected individuals than healthy persons but should still be offered

(84). A vaccine against HPV subtypes 16 and 18 is available to prevent cervical infection (85). This vaccine could conceivably prevent anal infections due to these oncogenic subtypes (although this is unproven), and thus might prevent anal cancer (86). To be effective, HBV and HPV vaccines would need to be administered before acquisition of these infections, which often occurs before acquisition of HIV. Thus, it remains unclear whether vaccination of persons who are already HIV-infected could prevent a sizeable number of liver or anal cancers. Among individuals with chronic liver disease, treatment of HCV and HBV infection may prevent progression to liver cancer (87).

Screening is targeted at identifying early-stage pre-malignant lesions, with the goal of eliminating those lesions to prevent progression to cancer. Only two of the non-AIDS-defining malignancies in Table 3 have known pre-malignant lesions that can be detected clinically and are thus amenable to screening intervention. For anal cancer, anal Pap smear screening can detect potentially pre-cancerous anal lesions (i.e., high-grade squamous intraepithelial lesions) that can be ablated with localized therapies (88). Issues regarding Pap smear screening include the high prevalence of anal intraepithelial neoplasia lesions potentially requiring intervention, uncertainty regarding the natural history of these lesions (i.e., rates of progression from high-grade squamous intraepithelial lesions to cancer), need for repeated screening to detect incident lesions, need for expertise in evaluating and treating pre-malignant lesions detected by Pap smears, and lack of proven effectiveness in reducing cancer burden (89). Nonetheless, under a broad range of assumptions, anal Pap smear screening in HIV-infected men-who-have-sex-with-men appears to be cost-effective (90). Testing of anal specimens for carcinogenic HPV genotypes may also be useful in risk stratification, as is the case for cervical cancer (91). Skin cancer screening can identify pre-malignant lesions, such as dysplastic nevi (a precursor to melanoma) and actinic keratoses (a precursor to squamous cell carcinoma). Given the simplicity and low cost of skin cancer screening, it seems feasible to incorporate it into periodic health examinations in HIV-infected persons. As in the transplant setting (92), HIV-infected patients with prior skin cancers should likely receive more intensive screening by dermatologists. Because the vast majority of skin cancer cases arise in non-Hispanic whites, it is reasonable to focus predominantly on this group.

Early detection has as its aim the detection of cancers at a stage when they are still localized and amenable to cure. The two screening modalities mentioned above, which have as their goal the detection of pre-malignant anal and skin lesions, would also detect cancers at a localized stage when site-directed treatment might be curative. For high-risk smokers (e.g., those with heavy long-term tobacco use or chronic obstructive pulmonary disease), lung cancer screening through the periodic use of chest radiographs or computed tomography scans can detect localized cancers. While potentially attractive, such screening is expensive, and these approaches are not yet demonstrated to be effective in the general population (93,94). Of note, while the higher risk of lung cancer in HIV-infected persons compared to uninfected persons increases the cost-effectiveness of screening, possibly lower sensitivity or specificity of diagnostic tests (e.g., due to a high frequency of non-specific findings on chest radiographs in HIV-infected persons) could reduce cost-effectiveness. Among patients with cirrhosis in the general population, periodic screening for liver cancer with serum alpha-fetoprotein testing and ultrasound has been advocated by some experts (95), and extension of such screening to HIV-infected persons may be warranted (96).

Conclusions

As the physicist Niels Bohr said, "Prediction is difficult, especially about the future." Nonetheless, for three reasons it is reasonable to predict that the burden of non-AIDS-defining cancer morbidity will rise over time in HIV-infected persons. As described above, for at least two cancers, incidence has already increased in recent years, perhaps due to immune-

modulating effects of HAART (Hodgkin lymphoma) or prolonged infection with an oncogenic virus (anal cancer). Second, because HIV-infected persons are now living longer, due to the beneficial effects of HAART, they are aging. Incidence of most cancers rises with age, due to an accumulation of DNA mutations from known carcinogenic exposures (e.g., tobacco smoke), the effects of chronic inflammation (e.g., hepatitis related to HCV infection), as well as from unknown or random events. For virtually all types of cancers—those where HIV-infected persons are frequently exposed to potent carcinogens, those where HIV exerts an additive effect on risk, even those where risk is the same as in the general population and HIV exerts no effect—the incidence will rise among HIV-infected persons due simply to aging. Third, prolonged survival attributable to HAART will increase the time during which HIV-infected persons are at risk of cancer, thus increasing the number of observed cases. In the absence of competing mortality from AIDS, HIV-infected persons have more opportunity to develop a cancer. It seems possible that these factors will remain relevant even if HAART is initiated at an earlier stage of HIV infection than currently recommended (97). Thus, the rising number of cases of non-AIDS-defining cancers will make prevention and treatment of these malignancies an increasing priority in HIV care.

As we enter the second decade of the HAART era, these considerations point to a need for additional research on the etiology of non-AIDS-defining cancers in HIV-infected persons. Ultimately, the goal of this research is to prevent cancer in HIV-infected individuals. By shedding light on immune-related and other pathways, the research may also help clarify the etiology of diverse malignancies in HIV-uninfected people.

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Figure 1.

Cancer incidence among people with AIDS in the U.S. (1984-2002). Incidence is shown as a function of calendar year of AIDS onset for Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), cervical cancer, and non-AIDS-defining cancers. Incidence estimates for each cancer are stacked on top of each other, to depict the proportion of total cancer incidence contributed by each cancer type. Data pertain to the two-year period following AIDS onset. Data are from the HIV/AIDS Cancer Match Study. The figure is reproduced with permission from Engels et al. (1).

Figure 2.

Hodgkin lymphoma risk among people with AIDS in the U.S. Risk is shown as a standardized incidence ratio (SIR), measuring risk relative to that in the general population. Panel A depicts SIRs as a function of year of AIDS onset. The smooth curve corresponds to a significant linear trend of increasing Hodgkin lymphoma risk during 1990-2002; the data points corresponding to AIDS onset in 2000-2002 are based on sparse numbers of people under follow-up. Panel B depicts SIRs as a function of CD4 count at AIDS onset (cells/mm³). The smooth curve corresponds to a model with a significant quadratic term, indicating maximum Hodgkin lymphoma risk at a CD4 count around 225-249 cells/mm³. Data are from the HIV/AIDS Cancer

Match Study. Panels are similar to figures presented in Engels et al. (1) and Biggar et al. (32).

Risk of selected non-AIDS-defining malignancies among HIV-infected persons in the U.S. during the HAART era

Malignancy	Risk factor	Proportion of all non-AIDS malignancies	Proportion of all non-AIDS malignancies	SIR (95%CI)*	Relationship with immunosuppressio n?	Increasing incidence over time?
Lung cancer	Tobacco	14%	23%	2.6 (2.1-3.2)	Uncertain	No
Hodgkin lymphoma	EBV	5%	8%	6.7 (4.5-9.5)	Yes, but non-linear	Yes
Anal cancer	HPV	2%	4%	9.1 (5.1-15)	Uncertain	Yes
Liver cancer	HCV, HBV, alcohol	2%	4%	3.1 (1.7-5.2)	Uncertain	No
Non-melanoma skin cancer	Ultraviolet radiation	?	?	-	Yes	No

Abbreviations: SIR standardized incidence ratio, CI confidence interval, EBV Epstein Barr virus, HPV human papillomavirus, HCV hepatitis C virus, HBV hepatitis B virus.

* Estimates are for people with AIDS in the United States during 1996-2002. The standardized incidence ratio is the observed incidence of the cancer in people with AIDS divided by the incidence expected based on general population rates. Data are from Engels et al. (1).

Table 2

Potential HIV-related immunologic mechanisms involved in development of selected non-AIDS-defining malignancies

Malignancy	Potential HIV-related immunologic mechanisms
Lung cancer	Chronic pulmonary inflammation, repeated infections
Hodgkin lymphoma	Immunosuppression, immune reconstitution
Anal cancer	Immunosuppression in relation to early-stage neoplasia, duration of immunosuppression
Liver cancer	Immunosuppression, duration of immunosuppression
Non-melanoma skin cancer	Immunosuppression

Table 3

Potential opportunities for prevention, screening, and early detection for selected non-AIDS-defining malignancies

Malignancy	Prevention	Screening	Early detection
Lung cancer	Smoking cessation	-	Chest radiography and computed tomography
Hodgkin lymphoma	-	-	-
Anal cancer	Reduced sexual exposures HPV vaccination	Anal Pap smears HPV DNA testing	Anal Pap smears
Liver cancer	Reduced sexual exposures Alcohol cessation HBV vaccination HCV and HBV treatment		AFP and ultrasound
Non-melanoma skin cancer	Reduced sun exposure	Skin examination	Skin examination

Abbreviations: HBV hepatitis B virus, HCV hepatitis C virus, AFP alpha-feto protein

Note: Not all interventions in the table are established as effective or cost-effective (see text).