Does HIV/AIDS Have a Biological Impact on the Risk of Human Papillomavirus–Related Cancers?

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HIV-related immunosuppression is a well-accepted, strong biological risk factor for two virus-associated cancers: Kaposi's sarcoma, which is associated with Kaposi's sarcoma–associated herpesvirus, and non-Hodgkin lymphoma, which is associated with Epstein–Barr virus. In fact, recognition of an extraordinarily high rate of Kaposi's sarcoma among men who have sex with men in New York and California during the early 1980s was one of the first indications of the existence of a human immunodeficiency virus (1–3). Soon thereafter, high rates of non-Hodgkin lymphoma in men who have sex with men were also recognized (4,5), and both Kaposi's sarcoma and non-Hodgkin lymphoma became designated as AIDS-defining malignancies in HIV-positive patients (6–8). It was not until the 1990s though that formal linkages between population-based AIDS registries and cancer registries were initiated (9,10). The AIDS–cancer match registry study in the United States (11,12), and similar studies in other countries (13–15), found that the risks for both Kaposi's sarcoma and non-Hodgkin lymphoma were increased by at least 100-fold in persons who developed AIDS compared with the general population (11,12). Furthermore, there were indications of a biological gradient—one of several criteria used to assess a possible causal relationship. Specifically, the risks for both Kaposi's sarcoma and non-Hodgkin lymphoma increased, and with lower $CD4^+$ T-cell count at time of AIDS onset (16) with increasing time after AIDS diagnosis (which is thought to be a surrogate indicator of diminishing immunity) (11,12).

Another virus-associated cancer, cervical cancer, has also been designated as an AIDS-defining malignancy. Cervical cancer is etiologically related to human papillomavirus and, because cervical cancer is the second most common cancer in women worldwide, the risk factors for cervical neoplasia are of substantial clinical and public health relevance. As a result, when the first reports of an association between HIV/AIDS and cervical disease were published in the late 1980s (17–19), they received considerable attention. They were also met with some skepticism (20). Commentators noted that cervical cancer was not a major cause of death in HIV-positive women, that most published data focused on precancerous cervical neoplasia and not invasive cancer, that several of the studies had important methodological limitations, and that cervical cancer and HIV share sexual risk factors (suggesting that behavioral factors might explain their association) (20). In fact, cervical cancer was not incorporated into the definition of AIDS until 1993 after additional reports indicated that HIV/AIDS and $CD4^+$ T-cell count were associated with precancerous cervical neoplasia (21) and after an extensive comment period to allow discussion of this controversial designation (22,23). Questions regarding whether there was a biological association between HIV/AIDS and invasive cervical cancer persisted.

The biological impact of HIV/AIDS on cervical cancer remained uncertain even after AIDS–cancer registry match studies reported fivefold or greater increased risks of cervical cancer in patients with AIDS compared with the general population (11,12,14,24). Investigators correctly noted that unlike the risks for Kaposi's sarcoma and non-Hodgkin lymphoma, risk for cervical cancer did not increase with increasing time after AIDS (24) and was not associated with $CD4^+$ T-cell count at the time of AIDS diagnosis (16)—evidence that the high rates of cervical cancer in women with AIDS might be unrelated to immunosuppression and, therefore, not biologically associated with HIV.

Similar results were found for other human papillomavirus–related cancers as well, including tumors of the anus, vagina, vulva, penis, and oropharynx. Each of these cancers has been shown to be statistically significantly more common in persons with AIDS than in the general population. According to a recent meta-analysis, for example, these relative risks (RRs) range from RR = 2.3 for oropharyngeal tumors to RR = 29 for anal cancer in AIDS–cancer registry match studies (25). However, there was little other evidence from registry-based studies that suggested a possible relation between human papillomavirus–related tumors and immunosuppression (16,24).

The accompanying article by Chaturvedi et al. (26) presents results from the most recent update of the AIDS–cancer match registry study. This study is by far the largest study of its type, with data from more than 499 230 persons who developed AIDS. More importantly, several of their findings suggest a possible association of human papillomavirus–related cancers with HIV-related immunosuppression. For the first time since the AIDS–cancer match registry study was initiated, the investigators reported that low $CD4^+$ T-cell count at the time of AIDS onset was statistically significantly associated with increased risk of anal cancer in men (P = .006) and had a suggestive, but non-statistically significant, association with risk of cervical cancer (P = .08). Similarly, increasing time after AIDS onset was associated with increased risks of invasive anal cancer (P = .04) and with in situ (but not invasive) carcinomas of the cervix (P = .06), vulva or vagina (P = .03), and penis (P = .03). These results were consistent with another recent report from the AIDS–cancer match registry study (27). In that study, the dataset was limited to several large HIV/AIDS registries in the United States that require reporting of patients with serologic evidence of HIV

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infection (as well as those already diagnosed with AIDS). The findings showed that the risk of cervical cancer was greater after a diagnosis of AIDS (RR = 5.3; 95% confidence interval [CI] = 2.0 to 12) than before a diagnosis of AIDS (RR = 2.6; 95% CI = 1.6 to 3.9), as were the risks for anal cancer (RR = 18 vs RR = 8.1) and oropharyngeal cancer (RR = 4.3 vs RR = 1.3), although only the latter reached statistical significance (27). Thus, both in Chaturvedi et al. and another recent report from the AIDS–cancer match registry study, there was evidence of a biological gradient of increasing risks of several (but not all) human papillomavirus–related cancers with increasing HIV-associated immunosuppression.

Additional evidence that immunosuppression may increase the risk of human papillomavirus–related cancers has come from studies of renal transplant patients (28–32). Renal transplant patients are iatrogenically immunosuppressed but, unlike HIV-positive patients, there is little reason to believe that they have high rates of sexually transmitted infections. A meta-analysis (25) of studies that linked transplant patient registries and cancer registries found a pattern that was similar to the pattern in AIDS–cancer registry match studies, with statistically significantly higher rates of cervical, anal, vulva or vagina, penis, and oropharyngeal tumors in transplant patients than in the general population. The results were highly consistent across the different transplant patient studies, and the strength of the associations were often strikingly similar in magnitude to those observed with AIDS.

Collectively, therefore, there is increasing evidence supporting the existence of a biological relationship between HIV/AIDS, and immunosuppression in general, with risk of human papillomavirus–associated cancers. If such a relationship exists, however, how might we address some of the seeming inconsistencies that have been reported? 1) The incidence of these cancers has not decreased during the highly active antiretroviral therapy (HAART) era and, in some cases (eg, anal and oropharyngeal cancer), may actually be increasing (26,33). In response, because of the more moderate effects of HIV-related immunosuppression on risk of HPV-related cancers than on Kaposi's sarcoma or non-Hodgkin lymphoma, the longer survival of HIV-positive patients related to HAART may have a proportionately greater impact on the risk of HPV-related cancers than the partial reversal of immunosuppression that occurs with HAART. 2) It has been more difficult to detect associations between markers of immune status (eg, increasing time from AIDS onset) and risk of human papillomavirus–related cancers than with risk of Kaposi's sarcoma and non-Hodgkin lymphoma (11, 12, 24). In response, the stronger associations of HIV/AIDS with Kaposi's sarcoma and non-Hodgkin lymphoma than with human papillomavirus–related cancers provide a broader range of relative risk values in which to detect a biological gradient (ie, incremental increases in relative risk of 100 or more versus threefold, respectively) and also greater statistical power. Kaposi's sarcoma and non-Hodgkin lymphoma may also develop more rapidly, requiring less follow-up time to assess associations. 3) Studies in Africa have given inconsistent results regarding the relation of HIV/AIDS with risk of cervical disease, even though both cervical cancer and HIV occur at high rates in Africa. In response, the estimated relative risks of all AIDS-defining cancers, including Kaposi's sarcoma, non-Hodgkin lymphoma, and cervical cancer, are lower in Africa (34,35). In this connection, it has been noted that differences in immune status between HIV-positive and HIV-negative individuals may not be as strong in settings with high rates of micronutrient deficiencies and chronic infections that are able to create a relative immunosuppressive state (36). Nonetheless, the only formal AIDS–cancer registry match study in Africa (35) found a statistically significant increased risk of cervical cancer in patients who developed AIDS.

The question remains, however, does the collective evidence now amount to proof of a biological relationship between HIV/AIDS and human papillomavirus–related cancers? Certainly, it is well established that the prevalence, incidence, and persistence of human papillomavirus and precancerous cervical neoplasia are strongly associated with $CD4^+$ T-cell count (immunosuppression) in HIV-positive women (37–40). It is also well established that the incidence of human papillomavirus–related cancers is increased severalfold in patients with HIV/AIDS, including cancers of the cervix, anus, vagina or vulva, penis, and oropharynx (25). The recent data from Chaturvedi et al. and other investigations from the AIDS-cancer match registry study (26,27) provide novel evidence relating several of these invasive cancers to the level of immunosuppression in patients with HIV/AIDS. Nonetheless, it must additionally be acknowledged that the associations between human papillomavirus–related cancers and markers of immunosuppression observed in Chaturvedi et al. were of moderate strength, varied between cancer types, and await confirmation. Although highly suggestive, therefore, the overall data fall short of proving a biological relationship between HIV/AIDS and human papillomavirus–related cancers. This argument does not change the likelihood that as the population of HIV-infected patients survives longer through use of HAART and increasingly enters the older age groups in which human papillomavirus–related cancer rates reach their peak, these tumors will represent an increasing clinical and public health burden (regardless of whether these are biological relationships). Consequently, cancer screening in adults with HIV/AIDS and human papillomavirus vaccination of HIV-positive individuals before their sexual debut (if proven effective) (41) will need to be priorities as HAART continues to transform HIV/AIDS into a chronic condition with a high rate of human papillomavirus–related and other cancers.

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