Are cancer outcomes worse in the presence of HIV infection?

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Commentary

As the 35 year-old epidemic of human immunodeficiency virus (HIV) infection in the United States has matured, effective treatment with highly active antiretroviral therapy (HAART) has decreased mortality from HIV-related causes and increased overall life expectancy. As a result, the cancer burden in the HIV-infected patient population has shifted from cancers strongly associated with immunodeficiency (i.e., acquired immunodeficiency syndrome [AIDS]-defining cancers) to those associated with aging. [1] Likewise, there has been an increase in mortality due to non-AIDS-defining cancers that are related to aging (e.g., colorectal, prostate, and breast cancers) or associated to a lesser degree with immunosuppression (e.g., anal and lung cancers). [2]

While these epidemiologic trends have been striking, a largely unanswered question is whether HIV-associated immunosuppression plays a direct role in altering cancer patient outcomes. More specifically, does immunosuppression from HIV infection impair a cancer patient's ability to control his or her tumor once it has been diagnosed, leading to a greater chance of relapse after cancer treatment and death due to the cancer?

Such an effect of HIV on cancer outcomes presupposes that the immune system can influence cancer progression. Experimental data have consistently suggested a role for the cells of the immune system in controlling the development of tumors. [3–5] Clinical data also provide evidence of the importance of the immune response in altering cancer outcomes, including the observation that the number of tumor-infiltrating lymphocytes is associated with patient prognosis for common malignancies such as melanoma and colorectal cancer. [6–9] Most notably, recent advances in cancer immunotherapies demonstrate that manipulation of the immune system can play a role in tumor progression. Specifically, monoclonal antibody preparations blocking immune checkpoint proteins that suppress T-cell responses, including cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) protein, induce tumor regression in a number of advanced malignancies and improve overall survival in patients with metastatic disease. [10–13]

The paper published by Marcus and colleagues in this issue of *Cancer Epidemiology, Biomarkers & Prevention* is a timely and welcome addition to the limited literature addressing the relationship between HIV-associated immunosuppression and cancer-specific

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outcomes. [14] This study compared the risk of death due to cancer (i.e., cancer-specific mortality) between HIV-infected cancer patients and HIV-uninfected cancer patients diagnosed between 1996 and 2011 within the Kaiser Permanente Northern and Southern California health maintenance organization networks. The cancer sites studied represent a spectrum including common solid organ tumors (i.e., prostate, lung and colorectal cancers) and infection-related cancers associated with HIV (i.e., anal cancer and Hodgkin lymphoma [HL]).

For each evaluated cancer, overall mortality within the 5 years following cancer diagnosis was higher in HIV-infected cancer patients compared to HIV-uninfected patients. This is not surprising, because HIV-infected patients have an additional serious medical condition—HIV infection itself—that can cause death unrelated to the presence of cancer. Marcus et al. also observed that cancer was the most common cause of death among the HIV-infected cancer patients for each of the cancers (comprising 61–84% of all deaths) except for HL (39% of deaths). More interestingly, the mortality due to cancer in the 5 years following diagnosis was substantially higher among the HIV-infected cancer patients (unadjusted hazard ratios [HRs] 1.2–2.2). To address potential biases that must be considered in outcome studies, the investigators accounted in their analysis for differences between HIV-infected and HIV-uninfected patients in crucial prognostic factors such as cancer stage and treatment. After these adjustments, cancer-specific mortality remained elevated in HIV-infected patients (adjusted HRs 1.3–2.1), although statistical significance was not uniformly attained for each cancer type. Of note, the findings by Marcus et al. regarding the association between HIV infection and cancer-specific mortality across a spectrum of cancer types are confirmed in a recent study that we conducted. [15] Other population-based studies also support the findings for lung cancer, providing consistent evidence that HIV-infected lung cancer patients have a higher risk of dying of their lung cancer than HIV-uninfected patients. [16]

A key consideration for future work in this area is the need for careful attention to potential cancer treatment differences between HIV-infected and HIV-uninfected patients that could explain survival deficits. In agreement with previous work, [17, 18] Marcus et al. observed that HIV-infected patients may receive a different regimen of cancer treatment. [14] For example, only 7% of HIV-infected HL patients received radiation therapy, compared to 27% of HIV-uninfected HL patients. HIV-infected cancer patients may be less likely than uninfected patients to receive appropriate cancer treatment because of greater co-morbidity and social problems that interfere with access to care (including drug abuse or lack of medical insurance). Although the authors adjusted for the type of cancer treatment in their analysis, the lack of granular data (i.e., dosage and number of cycles of chemotherapy or radiation) may have prevented fully accounting for treatment differences.

If future work supports these findings, the implication would be that immunity is directly linked not only to cancer incidence but also to control of cancer and survival. One crucial next step for assessing this hypothesis is the evaluation of cancer-specific outcomes in HIV-infected people in relation to sensitive clinical measures of immunosuppression (i.e., CD4 T-cell counts and HAART use). Along these lines, the Kaiser group previously demonstrated that, for non-Hodgkin lymphoma, cancer-specific survival was especially poor among those

HIV-infected patients who had very low CD4 T-cell counts (i.e., <200 cells/mm^3). [19] This type of information will be useful to demonstrate that the degree of immunosuppression is related to cancer outcomes in a dose-response manner. It would also support the clinical importance of providing effective HAART to all HIV-infected cancer patients, to reduce the risk of deaths from cancer as well as HIV infection.

In conclusion, the results reported by Marcus and colleagues support that HIV-infected cancer patients have poorer cancer-specific survival than HIV-uninfected patients, even after accounting for cancer stage and treatment. Future work should evaluate the association between HIV and cancer-specific mortality for additional types of cancer. Research utilizing more detailed cancer treatment data and biological measurements of immunosuppression is also needed. This question of whether cancer outcomes are worse in the presence of HIV infection is worthy of additional study as the number of patients diagnosed with both HIV and cancer continues to grow in the era of effective HAART. Furthermore, the intriguing possibility that immunosuppression worsens control of cancer points to the relevance of an intact immune system in HIV-uninfected cancer patients and highlights the promise of emerging immunotherapies.

Acknowledgments

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