Elevated Cancer-Specific Mortality Among HIV-Infected Patients in the United States

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A B S T R A C T

Purpose

Despite advances in the treatment of HIV, HIV-infected people remain at increased risk for many cancers, and the number of non-AIDS-defining cancers is increasing with the aging of the HIV-infected population. No prior study has comprehensively evaluated the effect of HIV on cancer-specific mortality.

Patients and Methods

We identified cases of 14 common cancers occurring from 1996 to 2010 in six US states participating in a linkage of cancer and HIV/AIDS registries. We used Cox regression to examine the association between patient HIV status and death resulting from the presenting cancer (ascertained from death certificates), adjusting for age, sex, race/ethnicity, year of cancer diagnosis, and cancer stage. We included 1,816,461 patients with cancer, 6,459 (0.36%) of whom were HIV infected.

Results

Cancer-specific mortality was significantly elevated in HIV-infected compared with HIV-uninfected patients for many cancers: colorectum (adjusted hazard ratio [HR], 1.49; 95% CI, 1.21 to 1.84), pancreas (HR, 1.71; 95% CI, 1.35 to 2.18), larynx (HR, 1.62; 95% CI, 1.06 to 2.47), lung (HR, 1.28; 95% CI, 1.17 to 1.39), melanoma (HR, 1.72; 95% CI, 1.09 to 2.70), breast (HR, 2.61; 95% CI, 2.06 to 3.31), and prostate (HR, 1.57; 95% CI, 1.02 to 2.41). HIV was not associated with increased cancer-specific mortality for anal cancer, Hodgkin lymphoma, or diffuse large B-cell lymphoma. After further adjustment for cancer treatment, HIV remained associated with elevated cancer-specific mortality for common non-AIDS-defining cancers: colorectum (HR, 1.40; 95% CI, 1.09 to 1.80), lung (HR, 1.28; 95% CI, 1.14 to 1.44), melanoma (HR, 1.93; 95% CI, 1.14 to 3.27), and breast (HR, 2.64; 95% CI, 1.86 to 3.73).

Conclusion

HIV-infected patients with cancer experienced higher cancer-specific mortality than HIV-uninfected patients, independent of cancer stage or receipt of cancer treatment. The elevation in cancer-specific mortality among HIV-infected patients may be attributable to unmeasured stage or treatment differences as well as a direct relationship between immunosuppression and tumor progression.

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INTRODUCTION

Infection with HIV increases the risk of cancer. HIV-infected individuals develop AIDS-defining cancers (ADCs) such as Kaposi sarcoma (KS) and non-Hodgkin lymphoma at substantially higher rates than HIV-uninfected individuals.^{1,2} Risk is also elevated for several non-AIDS-defining cancers (NADCs), including Hodgkin lymphoma (HL), anal cancer, and lung cancer.³⁻⁵

The link between HIV and cancer is attributable in large part to the effects of immunosuppression. Highly active antiretroviral therapy (HAART)

for HIV was introduced in the United States in 1996 and has led to improved immunocompetence and lower AIDS-related mortality.⁶ Changing cancer trends in the HIV-infected population have also paralleled the introduction of HAART, with ADC incidence decreasing sharply since 1996.^{7,8} However, even in the HAART era, immunosuppression remains an important risk factor for both ADCs and NADCs.⁹⁻¹¹

Relatively few data exist regarding the association between HIV and patient survival after a cancer diagnosis. Such a link is biologically plausible if an intact immune system helps control cancer after

treatment to prevent relapse. Alternatively, survival disparities could result from HIV-infected patients with cancer presenting with more advanced disease or not receiving recommended cancer treatment. The largest US study to date documented a decline in all-cause mortality among HIV-infected patients with cancer in New York corresponding with the introduction of HAART in 1996.¹² However, these HIV-infected patients with cancer continued to experience worse survival than HIV-uninfected patients with cancer, even during the HAART era. Clinic-based studies from Africa have also demonstrated poorer survival in HIV-infected patients with cancer and improved survival with HIV treatment.^{13,14}

Importantly, these studies lack data on cause of death. All-cause mortality in HIV-infected patients with cancer reflects multiple contributing causes of death, including HIV as well as cancer. Thus, it remains unclear whether HIV-related immunosuppression affects mortality specifically because of cancer. The impact of HIV on cancer outcomes is an increasingly important question. As HIV-specific mortality has declined in the HAART era, life expectancy has improved, and HIV-infected individuals are aging, which has substantially increased the cancer burden among HIV-infected individuals.^{15,16}

We hypothesized that HIV is associated with poor immune control of cancer and hence that HIV-infected patients with cancer would have an increased risk of dying as a result of their cancer. We therefore examined the association between HIV and cancer-specific mortality among patients in the United States for a range of cancer types diagnosed during the HAART era.

PATIENTS AND METHODS

We used data from the HIV/AIDS Cancer Match (HACM) study, a linkage of 14 population-based HIV and cancer registries in the United States (<http://hivmatch.cancer.gov/>).² Our study used data from six HACM sites that provided data on date and cause of death (Colorado, Connecticut, Georgia, Michigan, New Jersey, and Texas).

Individuals with invasive cancers recorded in these six cancer registries were included if they were diagnosed with cancer during the HAART era (1996 to present), years when HIV infection and AIDS diagnoses were both reportable conditions, and years when cancer registries had complete case ascertainment (included years of cancer diagnoses varied by cancer registry: Colorado [1996 to 2007], Connecticut [2002 to 2010], Georgia [2004 to 2008], Michigan [1996 to 2010], New Jersey [1996 to 2007], and Texas [1997 to 2009]). If an individual was diagnosed with multiple cancers in the HAART era, we considered only the first cancer. Our investigation focused on the 14 cancers most commonly observed in HIV-infected individuals: cancers of the oral cavity/pharynx, colorectum, anus, liver, pancreas, larynx, lung, breast, cervix, prostate, and kidney/renal pelvis, as well as HL, diffuse large B-cell lymphoma (DLBCL), and melanoma. We excluded KS because the vast majority of patients with KS are HIV infected, and patient cases not linked to their state HIV/AIDS registry likely harbored unreported HIV infection.

The primary outcome was death resulting from cancer after a cancer diagnosis (ie, cancer-specific mortality), ascertained by cancer registries through linkage to state or national mortality files. Specifically, for each cancer type evaluated, we assessed death resulting from that cancer, defined using the underlying cause of death recorded in the cancer registry. For individuals with colorectal cancer, deaths listed as resulting from anal cancer were considered cancer deaths and vice versa; in addition, deaths resulting from any lymphoma were classified as cancer deaths for patients with HL or DLBCL.

Individuals who were not linked to their state HIV/AIDS registry were considered HIV uninfected. For patients with cancer with a confirmed linkage to an HIV/AIDS registry, the patient was classified as HIV infected starting at either the date of HIV report or AIDS diagnosis in the

registry, whichever occurred earlier. If HIV infection was documented after cancer diagnosis, follow-up time starting at cancer diagnosis was considered HIV uninfected until HIV report or AIDS diagnosis, after which it was classified as HIV infected.

For HIV-infected and HIV-uninfected patients with cancer, we calculated rates of all-cause and cancer-specific death. For HIV-infected patients with cancer, we also calculated rates of HIV-specific death after cancer diagnosis, again using the underlying cause of death in the cancer registries. For each cancer type, mortality rates were indirectly standardized to the age distribution of the HIV-infected patients.

Cox regression was used to compare all-cause and cancer-specific mortality between HIV-infected and HIV-uninfected patients with cancer, treating HIV as a time-dependent covariate. Follow-up time for each patient with cancer started at cancer diagnosis and ended at the earlier of death or December of the most recent year of completed cancer registration (2007 to 2010 across included states). In analyses of cancer-specific mortality, patients dying as a result of causes other than the presenting cancer were censored. Models included adjustment for age and calendar year at cancer diagnosis, sex, race/ethnicity, and cancer stage. Cancer stage was defined using SEER program summary stage classification (local, regional, distant, or unknown).

In addition, three cancer registries (Connecticut, Michigan, and Texas) provided information on first-course cancer therapy. We used this information to define variables capturing receipt of any first-course cancer treatment (defined as reported receipt of any of following treatment modalities: surgery, radiation therapy, chemotherapy, or immunotherapy, with following exceptions: hormonal therapy was also considered treatment for breast and prostate cancers, and surgery was not considered treatment for lymphoma [HL or DLBCL]) and receipt of standard treatment modalities for local-stage cancer (defined as reported receipt of following treatment modalities: chemotherapy and radiation therapy [anal cancer], chemotherapy [DLBCL], surgery [colorectal, liver, and breast cancers], or radiation therapy or surgery [non-small-cell lung cancer]). To account for differences in standard treatment by histologic subtype, the definition for lung cancer was restricted to non-small-cell lung cancer (NSCLC). In sensitivity analyses restricted to these three registries, we examined whether the following altered the association between HIV and cancer-specific mortality: adjustment for receipt of any first-course cancer treatment, adjustment for receipt of standard treatment modalities among patients with local-stage cancer, and restriction to patients with local-stage cancer who received standard treatment modalities.

To assess whether the association between HIV and cancer-specific mortality changed over time after cancer diagnosis, we included an interaction term between follow-up time and HIV status. If the interaction was significant, we estimated hazard ratios (HRs) in different time intervals (< 1.00, 1.00 to 1.99, or ≥ 2.00 years after cancer diagnosis). All analyses were conducted using SAS software (version 9.3; SAS Institute, Cary, NC).

RESULTS

We included 1,816,461 patients with cancer from six US states, 6,459 (0.36%) of whom were HIV infected based on linkage to HIV/AIDS registries. HIV-infected patients with cancer were more likely to be male, nonwhite, and younger than HIV-uninfected patients (Table 1), largely reflecting demographic characteristics of the US HIV-infected population. The most common cancers in HIV-infected patients were DLBCL (25.8%), lung cancer (16.4%), and anal cancer (10.3%), whereas the most common cancers in HIV-uninfected patients were prostate (22.8%), breast (21.3%), and lung cancers (18.1%). Cancer stage at diagnosis was more advanced among HIV-infected patients, with 32.2% presenting with distant disease, compared with 17.7% of HIV-uninfected patients ($P < .01$). On the basis of data from three cancer registries ($n = 1,240,931$), HIV-infected patients were less likely than HIV-uninfected patients to receive any first-course cancer treatment (68.8% v 74.6%; $P < .01$).

Fig 1. Age-standardized mortality rates in HIV-infected and HIV-uninfected patients with cancer. For each cancer type, vertical bars correspond to age-standardized mortality rates for deaths resulting from cancer (blue bars), HIV/AIDS (gold bars), and other causes (gray bars). Results are shown separately for HIV-infected (+) and HIV-uninfected (−) patients with cancer. Age categories used to standardize HIV-uninfected to HIV-infected population were as follows: < 40, 40 to 49, 50 to 59, 60 to 69, and ≥ 70 years. DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma.

Most HIV-infected patients (91.2%) had prevalent HIV infection before cancer diagnosis. Furthermore, most HIV-infected patients (80.7%) had advanced immunosuppression, as indicated by an AIDS diagnosis on or before cancer diagnosis, although this proportion varied for NADCs (eg, 43.0% for breast cancer v 79.3% for anal cancer; [Appendix Table A1](#), online only). Because cervical cancer and DLBCL are ADCs, 100% of patients with these diseases had an AIDS diagnosis. Among 696 HIV-infected patients with cancer whose HIV was not documented before cancer diagnosis, the median time from cancer to HIV report or AIDS diagnosis was 0.75 years (interquartile range, 0.25 to 2.25 years).

[Figure 1](#) depicts age-adjusted mortality rates according to HIV status for each cancer type. All-cause mortality after cancer diagnosis was higher in HIV-infected than HIV-uninfected patients with cancer, partly reflecting HIV-specific mortality. Among HIV-infected patients with cancer, 42.1% of deaths resulted from HIV, although this proportion was particularly high for lymphomas (HL, 59.5%; DLBCL, 64.8%) and lower for common NADCs (breast, 25.7%; lung, 24.3%; colorectum, 32.8%). Notably, cancer-specific mortality after diagnosis (ie, blue bars in [Fig 1](#)) was also consistently higher in HIV-infected than HIV-uninfected patients with cancer, although differences seemed smaller for anal cancer, kidney/renal pelvic cancer, HL, and DLBCL.

HIV-infected patients with cancer experienced elevated overall mortality after cancer diagnosis compared with HIV-uninfected patients ([Table 2](#)), even after adjustment for patient characteristics, including cancer stage (adjusted HRs, 1.50 to 4.62). More notably, cancer-specific mortality was significantly elevated for seven of the 14 cancers: colorectum (HR, 1.49; 95% CI, 1.21 to 1.84), pancreas (HR, 1.71; 95% CI, 1.35 to 2.18), larynx (HR, 1.62; 95% CI, 1.06 to 2.47), lung (HR, 1.28; 95% CI, 1.17 to 1.39), melanoma (HR, 1.72; 95% CI, 1.09 to 2.70), breast (HR, 2.61; 95% CI, 2.06 to 3.31), and prostate

(HR, 1.57; 95% CI, 1.02 to 2.41). Cancer-specificity mortality was suggestively elevated for three additional cancers: oral cavity/pharynx (HR, 1.31; 95% CI, 0.94 to 1.83), liver (HR, 1.17; 95% CI, 0.99 to 1.39), and cervix (HR, 1.27; 95% CI, 0.95 to 1.70). No elevation in cancer-specific mortality among HIV-infected patients was noted for anal cancer, HL, or DLBCL. For certain cancers, we observed fewer than 10 cancer-attributed deaths among HIV-infected patients during recent years (2004 to 2010). Nonetheless, the pattern of excess cancer-specific mortality associated with HIV was similar from 2004 to 2010, and the association remained significant for common NADCs such as breast (HR, 3.43; 95% CI, 2.35 to 5.01), lung (HR, 1.38; 95% CI, 1.21 to 1.56), and colorectal cancers (HR, 2.01; 95% CI, 1.49 to 2.71).

Results from an analysis restricted to patients diagnosed with locoregional-stage cancer were consistent with an association between HIV infection and poorer cancer survival ([Appendix Table A2](#), online only). In fact, the association between HIV and elevated cancer-specific mortality was more pronounced for certain cancers (pancreas: HR, 2.22; melanoma: HR, 2.27).

The proportional hazards assumption was not violated for any cancer except DLBCL ($P = .01$ for interaction between HIV and follow-up time). Whereas no association between HIV and death resulting from DLBCL was observed during the 1 year after cancer diagnosis (HR, 0.99; 95% CI, 0.85 to 1.16), HIV-infected patients with DLBCL were less likely to have deaths attributed to cancer during the second year after diagnosis (HR, 0.60; 95% CI, 0.39 to 0.93) or subsequently (HR, 0.52; 95% CI, 0.31 to 0.86).

In the three states that provided data on cancer treatment, effect estimates were similar to those reported for all six states combined, and adjustment for receipt of cancer therapy had little effect on the association between HIV and cancer-specific mortality ([Table 3](#)). Interestingly, cervical cancer mortality was significantly elevated among

Table 1. Characteristics of Patients With Cancer According to HIV Status

Characteristic	HIV Infected (n = 6,459)		HIV Uninfected (n = 1,810,002)	
	No.	%	No.	%
Sex				
Female	1,464	22.7	851,720	47.1
Male	4,995	77.3	958,282	52.9
Age at diagnosis, years				
< 40	1,465	22.7	80,114	4.4
40-49	2,371	36.7	181,958	10.1
50-59	1,775	27.5	367,289	20.3
60-69	685	10.6	488,378	27.0
70-79	153	2.4	458,322	25.3
≥ 80	10	0.2	233,941	12.9
Race/ethnicity				
White, non-Hispanic	2,485	38.5	1,398,418	77.3
Black, non-Hispanic	2,928	45.3	208,485	11.5
Hispanic	936	14.5	146,773	8.1
Other	112	1.7	56,326	3.1
Stage at diagnosis				
Local	2,186	33.8	898,891	49.7
Regional	1,432	22.2	433,496	24.0
Distant	2,081	32.2	320,425	17.7
Unknown	760	11.8	157,190	8.7
Cancer site				
Oral cavity/pharynx	278	4.3	56,656	3.1
Colorectum	374	5.8	261,981	14.5
Anus	668	10.3	7319	0.4
Liver	316	4.9	29,952	1.7
Pancreas	103	1.6	54,231	3.0
Larynx	120	1.9	22,503	1.2
Lung	1,058	16.4	327,866	18.1
Melanoma	132	2.0	92,257	5.1
Breast	314	4.9	386,041	21.3
Cervix	238	3.7	28,722	1.6
Prostate	502	7.8	413,308	22.8
Kidney/renal pelvis	154	2.4	77,069	4.3
HL	535	8.3	17,254	1.0
DLBCL	1,667	25.8	34,843	1.9
First-course cancer treatment*				
Received	2,684	68.8	922,617	74.6
Did not receive	799	20.5	175,950	14.2
Treatment details missing	417	10.7	138,464	11.2
Year of diagnosis†				
1996-1999	1,264	19.6	410,969	22.7
2000-2003	1,729	26.8	507,304	28.0
2004-2007	2,516	39.0	632,537	35.0
2008-2010	950	14.7	259,192	14.3
Cancer registry‡				
Colorado	298	4.6	125,308	6.9
Connecticut	495	7.7	100,306	5.5
Georgia	538	8.3	122,603	6.8
Michigan	860	13.3	466,303	25.8
New Jersey	1,723	26.7	325,060	18.0
Texas	2,545	39.4	670,422	37.0

Abbreviations: HL, Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma.

*Nos. and percentages for receipt of first-course cancer treatment were restricted to states with available treatment data (Connecticut, Michigan, and Texas). Receipt of treatment was defined as reported receipt of any of following treatment modalities: surgery, radiation therapy, chemotherapy, or immunotherapy, with following exceptions: hormonal therapy was also considered treatment for breast and prostate cancers, and surgery was not considered treatment for lymphoma (HL or DLBCL).

†Based on criteria described in Patients and Methods; included years of cancer diagnoses varied by cancer registry: Colorado (1996-2007), Connecticut (2002-2010), Georgia (2004-2008), Michigan (1996-2010), New Jersey (1996-2007), and Texas (1997-2009).

HIV-infected women in these three registries, both before and after treatment adjustment (HR, 1.67; 95% CI, 1.17 to 2.37). We further restricted our analyses to patients with local-stage cancer. Although data were too sparse to analyze for certain cancers, results were consistent with the main analyses (Table 4). Among patients both diagnosed with local disease and reported to have received standard cancer treatment modalities, those with HIV infection still experienced elevated cancer-specific mortality for common NADCs such as breast cancer (HR, 3.02; 95% CI, 1.50 to 6.05) and NSCLC (HR, 1.88; 95% CI, 1.11 to 3.18).

DISCUSSION

This study documents that during the HAART era in the United States, HIV-infected patients with cancer had a higher risk of dying as a result of their cancer than HIV-uninfected patients. This association was present across a range of common malignancies. Our findings provide evidence that the well-established link between HIV and cancer risk extends to cancer survival as well.

Differences in cancer-specific mortality according to HIV status may be partly attributable to variation in patients' disease stage at presentation or treatment inequalities. In our study, HIV-infected patients with cancer had more advanced disease than HIV-uninfected patients with cancer. However, we still observed associations between HIV and cancer-specific mortality after adjusting for cancer stage. Moreover, in a sensitivity analysis restricted to patients with locoregional-stage disease, HIV remained associated with elevated cancer-specific mortality. We previously reported that HIV-infected patients were less likely than HIV-uninfected patients to receive cancer treatment.^{17,18} However, adjustment for cancer treatment did not materially alter our findings or account for the elevated cancer-specific mortality in HIV-infected patients. Analyses restricted to those with local-stage cancer who received standard treatment modalities provided further evidence for a role of HIV independent of cancer stage or treatment differences.

Immunosuppression, whether in the context of HIV infection or organ transplantation, increases risk most markedly for cancers arising from infections.^{1,19} Given our findings, we speculate that a more overarching mechanism may exist whereby immunosuppression alters tumor progression, regardless of the factors responsible for tumor development. Additional evidence for this hypothesis is provided by the observation that lower numbers of tumor-infiltrating lymphocytes, including T cells, have been associated with poor prognosis in clinical studies of patients with common malignancies, including melanoma and colorectal cancer.²⁰⁻²² Clinical trials have demonstrated that manipulation of the immune system (ie, adoptive T-cell therapy or administration of monoclonal antibodies) can affect cancer survival.²³⁻²⁸ Furthermore, the HIV transactivator of transcription protein may promote angiogenesis, a process crucial for tumor growth, by mimicking the activity of vascular endothelial growth factor.²⁹⁻³¹

To our knowledge, our study is the largest and most systematic evaluation of survival after a cancer diagnosis among HIV-infected patients, and the use of registry data allowed for population-based assessment of the relationship between HIV and cancer-specific mortality. In agreement with our results, a US population-based study reported that HIV infection was associated with elevated lung cancer–

Table 2. Association of HIV With All-Cause and Cancer-Specific Mortality According to Year of Cancer Diagnosis

Cancer Diagnosis	1996 to 2010						2004 to 2010		
	Total Deaths	All-Cause Mortality		Cancer Deaths	Cancer-Specific Mortality		Cancer Deaths	Cancer-Specific Mortality	
		HR	95% CI		HR	95% CI		HR	95% CI
Oral cavity/pharynx									
HIV infected	154	2.46	2.09 to 2.88	35	1.31	0.94 to 1.83	16	1.11	0.67 to 1.81
HIV uninfected	24,440	1.00	Referent	8,608	1.00	Referent	3,025	1.00	Referent
Colorectum									
HIV infected	183	2.26	1.95 to 2.61	86	1.49	1.21 to 1.84	44	2.01	1.49 to 2.71
HIV uninfected	117,523	1.00	Referent	68,138	1.00	Referent	21,344	1.00	Referent
Anus									
HIV infected	268	1.86	1.60 to 2.16	79	0.97	0.75 to 1.25	33	0.90	0.61 to 1.33
HIV uninfected	2,560	1.00	Referent	1,321	1.00	Referent	458	1.00	Referent
Liver									
HIV infected	257	1.50	1.32 to 1.70	137	1.17	0.99 to 1.39	83	1.13	0.91 to 1.40
HIV uninfected	22,882	1.00	Referent	15,769	1.00	Referent	7,532	1.00	Referent
Pancreas									
HIV infected	89	1.84	1.49 to 2.26	67	1.71	1.35 to 2.18	43	1.71	1.27 to 2.31
HIV uninfected	45,274	1.00	Referent	38,015	1.00	Referent	16,523	1.00	Referent
Larynx									
HIV infected	81	2.70	2.17 to 3.37	22	1.62	1.06 to 2.47	7	1.58	0.75 to 3.34
HIV uninfected	10,092	1.00	Referent	3,428	1.00	Referent	1,167	1.00	Referent
Lung									
HIV infected	907	1.85	1.73 to 1.97	517	1.28	1.17 to 1.39	239	1.38	1.21 to 1.56
HIV uninfected	252,455	1.00	Referent	201,793	1.00	Referent	77,836	1.00	Referent
Melanoma									
HIV infected	47	3.56	2.67 to 4.74	19	1.72	1.09 to 2.70	8	1.55	0.77 to 3.10
HIV uninfected	17,601	1.00	Referent	8,500	1.00	Referent	2,808	1.00	Referent
Breast									
HIV infected	144	4.62	3.92 to 5.45	68	2.61	2.06 to 3.31	27	3.43	2.35 to 5.01
HIV uninfected	80,628	1.00	Referent	40,360	1.00	Referent	10,001	1.00	Referent
Cervix									
HIV infected	123	2.50	2.08 to 2.99	48	1.27	0.95 to 1.70	23	1.39	0.91 to 2.11
HIV uninfected	8,928	1.00	Referent	5,472	1.00	Referent	1,910	1.00	Referent
Prostate									
HIV infected	104	2.59	2.14 to 3.14	21	1.57	1.02 to 2.41	6	1.21	0.54 to 2.69
HIV uninfected	80,429	1.00	Referent	19,840	1.00	Referent	4,434	1.00	Referent
Kidney/renal pelvis									
HIV infected	68	2.36	1.86 to 3.00	21	1.17	0.76 to 1.80	10	1.30	0.70 to 2.41
HIV uninfected	27,465	1.00	Referent	15,674	1.00	Referent	5,550	1.00	Referent
HL									
HIV infected	262	4.19	3.65 to 4.81	35	0.86	0.61 to 1.21	15	1.05	0.62 to 1.78
HIV uninfected	3,242	1.00	Referent	2,011	1.00	Referent	680	1.00	Referent
DLBCL									
HIV infected	1,148	3.55	3.31 to 3.81	212	0.88	0.76 to 1.01	71	0.86	0.67 to 1.10
HIV uninfected	16,349	1.00	Referent	11,092	1.00	Referent	3,925	1.00	Referent

NOTE. Cox regression models included following covariates: age at cancer diagnosis (< 40, 40-49, 50-59, 60-69, or ≥ 70 years), sex (male or female), year of cancer diagnosis (1996-1999, 2000-2003, 2004-2007, or 2008-2010), race/ethnicity (white non-Hispanic, black non-Hispanic, Hispanic, or other), and cancer stage at diagnosis (local, regional, distant, or unknown).
Abbreviations: DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; HR, hazard ratio.

specific mortality among elderly patients with NSCLC.³² Data for lymphoid malignancies are conflicting. In one study, HIV-infected patients with non-Hodgkin lymphoma experienced elevated cancer-specific mortality, although this was limited to patients with more severe immunosuppression.³³ Further supporting the importance of immunosuppression, lack of effective antiretroviral therapy and low CD4 T-cell counts have been associated with poor response to chemotherapy and all-cause mortality among HIV-infected patients with lymphoma.³⁴⁻³⁹ In contrast, a recent study of patients with HL using

SEER cancer registry data reported that cancer-specific mortality did not differ by HIV status, consistent with our results.⁴⁰

Our estimates of the association between HIV and cancer-specific mortality were generated in the presence of other causes of death. One particularly important competing risk, present only in HIV-infected persons, is death resulting from HIV. The association between HIV and cancer-specific mortality may be distorted if deaths resulting from cancer are not independent of competing causes of death (ie, if HIV-infected patients with cancer who died as a result of

Table 3. Association of HIV With Cancer-Specific Mortality Adjusted for Receipt of First-Course Cancer Treatment

Cancer Diagnosis	Cancer Deaths	No Treatment Adjustment		Treatment Adjustment	
		HR	95% CI	HR	95% CI
Oral cavity/pharynx					
HIV infected	17	1.15	0.72 to 1.86	1.19	0.74 to 1.92
HIV uninfected	6,102	1.00	Referent	1.00	Referent
Colorectum					
HIV infected	62	1.46	1.14 to 1.87	1.40	1.09 to 1.80
HIV uninfected	46,349	1.00	Referent	1.00	Referent
Anus					
HIV infected	49	0.84	0.61 to 1.15	0.84	0.61 to 1.15
HIV uninfected	919	1.00	Referent	1.00	Referent
Liver					
HIV infected	88	1.12	0.91 to 1.38	1.10	0.89 to 1.36
HIV uninfected	11,928	1.00	Referent	1.00	Referent
Pancreas					
HIV infected	38	1.86	1.35 to 2.55	1.85	1.34 to 2.54
HIV uninfected	25,823	1.00	Referent	1.00	Referent
Larynx					
HIV infected	12	1.56	0.88 to 2.76	1.54	0.87 to 2.72
HIV uninfected	2,412	1.00	Referent	1.00	Referent
Lung					
HIV infected	290	1.32	1.17 to 1.48	1.28	1.14 to 1.44
HIV uninfected	142,149	1.00	Referent	1.00	Referent
Melanoma					
HIV infected	14	1.91	1.13 to 3.23	1.93	1.14 to 3.27
HIV uninfected	5,956	1.00	Referent	1.00	Referent
Breast					
HIV infected	32	2.62	1.85 to 3.71	2.64	1.86 to 3.73
HIV uninfected	28,346	1.00	Referent	1.00	Referent
Cervix					
HIV infected	32	1.66	1.17 to 2.36	1.67	1.17 to 2.37
HIV uninfected	3,935	1.00	Referent	1.00	Referent
Prostate					
HIV infected	12	1.79	1.01 to 3.15	1.64	0.93 to 2.89
HIV uninfected	13,744	1.00	Referent	1.00	Referent
Kidney/renal pelvis					
HIV infected	18	1.33	0.83 to 2.11	1.15	0.73 to 1.84
HIV uninfected	11,515	1.00	Referent	1.00	Referent
HL					
HIV infected	27	1.07	0.72 to 1.58	1.08	0.73 to 1.60
HIV uninfected	1,428	1.00	Referent	1.00	Referent
DLBCL					
HIV infected	129	0.85	0.71 to 1.02	0.85	0.71 to 1.02
HIV uninfected	7,760	1.00	Referent	1.00	Referent

NOTE. Cox regression models included following covariates: age at cancer diagnosis (< 40, 40-49, 50-59, 60-69, or ≥ 70 years), sex (male or female), year of cancer diagnosis (1996-1999, 2000-2003, 2004-2007, or 2008-2010), race/ethnicity (white non-Hispanic, black non-Hispanic, Hispanic, or other), cancer stage at diagnosis (local, regional, distant, or unknown), and receipt of any first-course cancer treatment (defined as reported receipt of any of following treatment modalities: surgery, radiation therapy, chemotherapy, or immunotherapy, with following exceptions: hormonal therapy was also considered treatment for breast and prostate cancers, and surgery was not considered treatment for lymphoma [HL or DLBCL]). Data restricted to Connecticut, Michigan, and Texas.

Abbreviations: DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; HR, hazard ratio.

HIV would have been those most likely to die as a result of cancer). No method is able to accurately reassign cause of death, because one cannot observe whether an individual who died as a result of HIV would have died as a result of cancer instead. Despite this uncertainty, our use of Cox regression was appropriate, because rather than estimate the absolute risk of cancer death, we sought to measure an etiologic association between HIV and cancer-specific mortality.⁴¹

Although overall survival among HIV-infected patients has improved during the HAART era,⁶ HIV remained a key cause of death

among HIV-infected patients with cancer in our study. This highlights the potential benefit of early HAART initiation to maintain adequate levels of immunocompetence throughout cancer therapy. Furthermore, if our hypothesis regarding the adverse impact of immunosuppression on tumor progression is correct, early HAART initiation could decrease not only HIV-specific mortality but also cancer-specific mortality.

We acknowledge the limitations of our study. Treatment data from registries lacked detail and may have been incomplete, so it is uncertain whether our analyses could completely adjust for

Table 4. Association of HIV With Cancer-Specific Mortality for Patients Diagnosed With Local-Stage Disease According to Receipt of Standard Cancer Treatment

Cancer Diagnosis	Adjusted for Treatment			Restricted Analyses*		
	Cancer Deaths	HR	95% CI	Cancer Deaths	HR	95% CI
Colorectum						
HIV infected	13	2.20	1.22 to 4.00	—†	—	—
HIV uninfected	5,932	1.00	Referent	—	—	—
Anus						
HIV infected	17	1.41	0.76 to 2.59	13	1.59	0.73 to 3.46
HIV uninfected	255	1.00	Referent	199	1.00	Referent
Liver						
HIV infected	23	0.96	0.62 to 1.47	9	2.79	1.43 to 5.44
HIV uninfected	3,443	1.00	Referent	642	1.00	Referent
NSCLC						
HIV infected	27	1.81	1.21 to 2.70	15	1.88	1.11 to 3.18
HIV uninfected	15,410	1.00	Referent	8,508	1.00	Referent
Breast						
HIV infected	9	2.61	1.36 to 5.03	8	3.02	1.50 to 6.05
HIV uninfected	6,550	1.00	Referent	5,122	1.00	Referent
DLBCL						
HIV infected	23	1.37	0.88 to 2.13	13	1.11	0.63 to 1.95
HIV uninfected	1,618	1.00	Referent	821	1.00	Referent

NOTE. Cox regression models included following covariates: age at cancer diagnosis (< 40, 40-49, 50-59, 60-69, or ≥ 70 years), sex (male or female), year of cancer diagnosis (1996-1999, 2000-2003, 2004-2007, or 2008-2010), race/ethnicity (white non-Hispanic, black non-Hispanic, Hispanic, or other), and receipt of standard cancer treatment (defined as reported receipt of following treatment modalities: chemotherapy and radiation therapy [anal cancer], chemotherapy [DLBCL], surgery [colorectum, liver, and breast cancers], or radiation therapy or surgery [NSCLC]). Data restricted to Connecticut, Michigan, and Texas.

Abbreviations: DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; NSCLC non-small-cell lung cancer.

*Restricted to patients with local-stage cancer with reported receipt of standard cancer treatment.

†Estimates reported only for cancers with at least five events in HIV-infected group.

differences between HIV-infected and HIV-uninfected patients. We did not have prognostic information beyond anatomic stage provided by cancer registries. However, results were similar when we restricted analyses to patients with locoregional disease. In addition, a small proportion of patients with cancer had HIV reported after cancer diagnosis (Appendix Table A1), and it is possible that delays in HIV reporting led to a portion of their follow-up time being incorrectly classified as HIV uninfected. We also lacked data on measures of immunosuppression (eg, CD4 T-cell count, HIV viral load, HAART use).

Finally, assessment of cancer-specific mortality relied on the cause of death provided on the death certificate, opening up the potential for misclassification. We believe that reported causes of death were generally accurate. Researchers from our group previously used both cause of death specified on death certificates⁴² and population-attributable risk methods not relying on death certificates¹⁶ to quantify cancer deaths among HIV-infected patients in HACM. Both methods yielded a similar proportion of overall cancer deaths and deaths resulting from NADCs in patients with AIDS in the HAART era. Nonetheless, it is possible that clinicians may have miscoded some cancer deaths as resulting from AIDS, especially for malignancies strongly linked to HIV infection. If present, this miscoding could have partly obscured an association between HIV and cancer-specific mortality.

Of interest, cancers for which cancer-specific mortality was not associated with HIV status (ie, anal cancer, HL, DLBCL) were also cancers for which nearly half of overall mortality was attributed to HIV. DLBCL was the only malignancy that violated the proportional hazards assumption. The pattern of HIV-infected patients with DLBCL being less likely to die as a result of their lymphoma after the

first year after cancer diagnosis could be the result of an increase in competing risk of death resulting from HIV or potentially an increasing likelihood for physicians to code deaths as attributable to AIDS with longer time after DLBCL diagnosis.

In conclusion, HIV-infected patients with cancer are more likely to die as a result of their cancer than patients without HIV. Our results suggest that this difference not only is related to advanced tumor stage or lack of cancer treatment but also reflects an effect of immunosuppression on cancer outcomes. Despite the biologic plausibility of a role for immunosuppression in influencing tumor outcome, future clinical and laboratory studies are needed to formally evaluate this hypothesis. The public health importance of outcomes in patients diagnosed with both HIV and cancer will continue to grow as the number of patients diagnosed with these two diseases increases.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Elevated Cancer-Specific Mortality Among HIV-Infected Patients in the United States

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Appendix**Table A1.** Distribution of HIV/AIDS Diagnoses Relative to Date of Cancer Diagnosis

Cancer Diagnosis	Total	HIV Before, No AIDS After Cancer No. (%)	HIV Before, AIDS After Cancer No. (%)	AIDS Before Cancer No. (%)	HIV (no AIDS) After Cancer No. (%)	HIV and AIDS After Cancer No. (%)
Oral cavity/pharynx	278	39 (14.0)	20 (7.2)	179 (64.4)	10 (3.6)	30 (10.8)
Colorectum	374	62 (16.6)	25 (6.7)	210 (56.2)	39 (10.4)	38 (10.2)
Anus	668	27 (4.0)	43 (6.4)	530 (79.3)	18 (2.7)	50 (7.5)
Liver	316	58 (18.4)	7 (2.2)	223 (70.6)	13 (4.1)	15 (4.8)
Pancreas	103	25 (24.3)	1 (1.0)	71 (68.9)	3 (2.9)	3 (2.9)
Larynx	120	15 (12.5)	6 (5.0)	78 (65.0)	5 (4.2)	16 (13.3)
Lung	1,058	156 (14.7)	47 (4.4)	765 (72.3)	43 (4.1)	47 (4.4)
Melanoma	132	20 (15.2)	5 (3.8)	73 (55.3)	17 (12.9)	17 (12.9)
Breast	314	55 (17.5)	31 (9.9)	135 (43.0)	43 (13.7)	50 (15.9)
Cervix*	238	—	—	238 (100)	—	—
Prostate	502	107 (21.3)	12 (2.4)	262 (52.2)	65 (13.0)	56 (11.2)
Kidney/renal pelvis	154	34 (22.1)	12 (7.8)	70 (45.5)	20 (13.0)	18 (11.7)
HL	535	53 (9.9)	39 (7.3)	363 (67.9)	18 (3.4)	62 (11.6)
DLBCL*	1,667	—	—	1,667 (100)	—	—

Abbreviations: DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma.

*All HIV-infected patients with cervical cancer and DLBCL were classified as having AIDS, because these are AIDS-defining malignancies.

Table A2. Association of HIV With Cancer-Specific Mortality for Patients With Localized or Regional-Stage Disease

Cancer Diagnosis	All Stages at Presentation			Localized or Regional Disease		
	Cancer Deaths	HR	95% CI	Cancer Deaths	HR	95% CI
Oral cavity/pharynx						
HIV infected	35	1.31	0.94 to 1.83	24	1.36	0.91 to 2.03
HIV uninfected	8,608	1.00	Referent	5,919	1.00	Referent
Colorectum						
HIV infected	86	1.49	1.21 to 1.84	43	1.75	1.30 to 2.36
HIV uninfected	68,138	1.00	Referent	32,523	1.00	Referent
Anus						
HIV infected	79	0.97	0.75 to 1.25	53	0.98	0.71 to 1.35
HIV uninfected	1,321	1.00	Referent	824	1.00	Referent
Liver						
HIV infected	137	1.17	0.99 to 1.39	68	1.24	0.97 to 1.57
HIV uninfected	15,769	1.00	Referent	7,914	1.00	Referent
Pancreas						
HIV infected	67	1.71	1.35 to 2.18	17	2.22	1.38 to 3.57
HIV uninfected	38,015	1.00	Referent	13,811	1.00	Referent
Larynx						
HIV infected	22	1.62	1.06 to 2.47	14	1.62	0.96 to 2.76
HIV uninfected	3,428	1.00	Referent	2,403	1.00	Referent
Lung						
HIV infected	517	1.28	1.17 to 1.39	165	1.44	1.24 to 1.68
HIV uninfected	201,793	1.00	Referent	67,991	1.00	Referent
Melanoma						
HIV infected	19	1.72	1.09 to 2.70	10	2.27	1.22 to 4.22
HIV uninfected	8,500	1.00	Referent	4,542	1.00	Referent
Breast						
HIV infected	68	2.61	2.06 to 3.31	47	2.61	1.96 to 3.48
HIV uninfected	40,360	1.00	Referent	26,860	1.00	Referent
Cervix						
HIV infected	48	1.27	0.95 to 1.70	34	1.48	1.05 to 2.08
HIV uninfected	5,472	1.00	Referent	3,549	1.00	Referent
Prostate						
HIV infected	21	1.57	1.02 to 2.41	8	1.55	0.77 to 3.10
HIV uninfected	19,840	1.00	Referent	9,211	1.00	Referent
Kidney/renal pelvis						
HIV infected	21	1.17	0.76 to 1.80	8	1.34	0.67 to 2.68
HIV uninfected	15,674	1.00	Referent	5,892	1.00	Referent
HL						
HIV infected	35	0.86	0.61 to 1.21	5	0.66	0.27 to 1.61
HIV uninfected	2,011	1.00	Referent	673	1.00	Referent
DLBCL						
HIV infected	212	0.88	0.76 to 1.01	64	1.20	0.93 to 1.56
HIV uninfected	11,092	1.00	Referent	3,926	1.00	Referent

NOTE. Cox regression models included following covariates: age at cancer diagnosis (< 40, 40-49, 50-59, 60-69, or ≥ 70 years), sex (male or female), year of cancer diagnosis (1996-1999, 2000-2003, 2004-2007, or 2008-2010), race/ethnicity (white non-Hispanic, black non-Hispanic, Hispanic, or other), and cancer stage at diagnosis (local, regional, distant, or unknown).

Abbreviations: DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; HR, hazard ratio.