Original Article

Advanced Stage at Diagnosis and Elevated Mortality Among US Patients With Cancer Infected With HIV in the National Cancer Data Base

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BACKGROUND: People living with HIV (PLWH) are at an increased risk of developing several cancers, but to the authors' knowledge less is known regarding how HIV impacts the rate of progression to advanced cancer or death. **METHODS:** The authors compared stage of disease at the time of presentation and mortality after diagnosis between 14,453 PLWH and 6,368,126 HIV-uninfected patients diagnosed with cancers of the oral cavity, stomach, colorectum, anus, liver, pancreas, lung, female breast, cervix, prostate, bladder, kidney, and thyroid and melanoma using data from the National Cancer Data Base (2004-2014). Polytomous logistic regression and Cox proportional hazards regression were used to evaluate the association between HIV, cancer stage, and stage-adjusted mortality after diagnosis, respectively. Regression models accounted for the type of health facility at which cancer treatment was administered and the type of individual health insurance. **RESULTS:** HIV-infected patients with cancer were found to be more likely to be uninsured (HIV-infected: 5.0% vs HIV-uninfected: 3.3%; $P < .0001$) and were less likely to have private health insurance (25.4% vs 44.7%; $P < .0001$). Compared with those not infected with HIV, the odds of being diagnosed at an advanced stage of disease were significantly elevated in PLWH for melanoma and cancers of the oral cavity, liver, female breast, prostate, and thyroid (odds ratio for stage IV vs stage I range, 1.24-2.06). PLWH who were diagnosed with stage I to stage III disease experienced elevated mortality after diagnosis across 13 of the 14 cancer sites evaluated, with hazard ratios ranging from 1.20 (95% CI, 1.14-1.26) for lung cancer to 1.85 (95% CI, 1.68-2.04), 1.85 (95% CI, 1.51-2.27), and 2.93 (95% CI, 2.08-4.13), respectively, for cancers of the female breast, cervix, and thyroid. **CONCLUSIONS:** PLWH were more likely to be diagnosed with advanced-stage cancers and to experience elevated mortality after a cancer diagnosis, even after accounting for health care–related factors. ***Cancer*** **2019;125:2868-2876**.

KEYWORDS: cancer patient mortality, cancer stage, health insurance and mortality, HIV and cancer, National Cancer Data Base.

INTRODUCTION

People living with HIV (PLWH) have an elevated risk of certain cancer types, particularly those caused by viral coinfections.[1-9] Rates of many infection-associated cancers among PLWH have declined after the widespread availability of highly active antiretroviral therapy (HAART) to restore patient immunity, although the risk remains elevated compared with HIV-uninfected individuals.[10-13] Unlike infection-associated cancers, some non–infection-related cancers such as those of the prostate, female breast, and colon do not occur at elevated rates in PLWH.[14] Nevertheless, these cancers are becoming increasingly prevalent among PLWH because of the widespread dissemination of HAART, which permits patients with HIV to live to older ages when cancers are more common.[15,16] This raises the important question of whether HIV-related immunosuppression is associated with tumors progressing to higher stages before being diagnosed or resulting in poorer outcomes after diagnosis.

Both advanced stage of disease at the time of presentation and elevated mortality after diagnosis can reflect tumor aggressiveness, and recent data have suggested that immunosuppressed patients fare worse on both

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metrics. A prior registry-based study demonstrated that PLWH were more likely to be diagnosed with distant-stage cancers of the lung, female breast, prostate, and bladder and melanoma.[17] Stage-adjusted mortality after a cancer diagnosis also was elevated in HIV-infected patients across a range of sites, including cancers of the colorectum, pancreas, larynx, lung, female breast, and prostate, and melanoma.[18] It is plausible that advanced-stage disease and elevated mortality after a cancer diagnosis among PLWH are related to the biological effects of HIV-associated immunosuppression.

However, the more advanced-stage cancers and elevated mortality reported among PLWH also could be related to receipt of suboptimal health care, a possibility supported by mounting data that PLWH are less likely to receive cancer treatment.[19,20] Available data have not been able to disentangle these possibilities. To begin addressing this issue of suboptimal health care, we evaluated the association between HIV, cancer stage at presentation, and mortality after a cancer diagnosis after accounting for the type of treating health facility and reported individual health insurance using data from >6 million US patients with cancer from the National Cancer Data Base (NCDB).

MATERIALS AND METHODS

The NCDB is a nationwide, hospital-based registry database jointly sponsored by the American Cancer Society and the American College of Surgeons. Using the NCDB, we ascertained the following primary, malignant cancers occurring in adults (those aged ≥18 years) between 2004 and 2014: oral cavity, pharynx, and/or larynx (*International Classification of Diseases for Oncology, 3rd Edition* [ICD-O-3] topography codes C000-C009, C019-C069, C079-C099, C100-C109, C110-C119, C129-C140, C142, C148, and C320-C329); stomach (ICD-O-3 codes C160-C169); colorectum (ICD-O-3 codes C180-C189, C199, and C209); anus (ICD-O-3 codes C210 and C218); liver (ICD-O-3 code C220); pancreas (ICD-O-3 codes C250-C259); lung (ICD-O-3 codes C340-C349); female breast (ICD-O-3 codes C500-C509); cervix (ICD-O-3 codes C530-C539); prostate (ICD-O-3 code C619); bladder (ICD-O-3 codes C670-C679); kidney (ICD-O-3 codes C649 and C659); and thyroid (ICD-O-3 code C739) and melanoma (ICD-O-3 codes C440-C449 with histology codes 8720-8790). Cancers with the following histology codes were excluded: 9050 to 9055, 9140, and 9590 to 9989. Patients with an unknown stage of disease, unknown date of diagnosis, or unknown last date of contact also were excluded.

The HIV status of each patient at the time of cancer diagnosis was defined using *International Classification of Diseases, Ninth Revision* (ICD-9) codes, with HIV positivity defined as the presence of codes 04200 to 04499, 07953, or V08. Cancer stage at the time of presentation was defined as stages I, II, III, or IV using the collaborative staging algorithm from the sixth edition of the American Joint Committee on Cancer (AJCC) (https://cancerstaging.org/cstage/Pages/default.aspx). Factors related to health care were ascertained from the NCDB, including data regarding the type of health facility at which cancer care was administered (community center, comprehensive community center, teaching/research institution, National Cancer Institute network cancer center, integrated network, or other/unknown, as defined by the Commission on Cancer[21]) and the type of reported health insurance (private, Medicaid, Medicare, no insurance, or other government insurance). We hypothesized that the type of treating health facility reflects an important aspect of the quality of care received, whereas individual health insurance can influence a patient's access to care.

Statistical Analysis

Polytomous logistic regression was used to estimate the association between HIV status and cancer stage at the time of presentation (with AJCC stage I as the referent group), adjusting for patient sex (male vs female), age (18-44 years, 45-54 years, 55-64 years, or ≥65 years), race (non-Hispanic white, black, Hispanic, other, or missing data), calendar year of cancer diagnosis (2004-2006, 2007-2010, or 2011-2014), and median household income by zip code (<$38,000, $38,000-$47,999, $48,000-$62,999, ≥$63,000, or missing data). Analyses were conducted separately for each cancer site. *P* values for trend were calculated by fitting logistic regression models with stage categorized as an ordinal variable, adjusting for the covariates listed above. To further assess whether any associations between HIV and cancer stage were attributable to factors related to suboptimal care, we adjusted for the type of health facility at which cancer treatment was received and the type of individual health insurance.

We next evaluated whether HIV was associated with overall mortality using Cox proportional hazards regression. Follow-up for each patient with cancer was calculated from the date of the cancer diagnosis to the date of death from any cause, with follow-up ending in 2014. Cases diagnosed between 2013 and 2014 were excluded to ensure adequate follow-up time to ascertain mortality. These mortality analyses were limited to patients with stage I to

stage III disease due to the heterogeneity of disease burden, treatment approaches, and outcomes that occur in patients with metastatic (stage IV) disease. Analyses were adjusted for age, sex, race, calendar year of cancer diagnosis, median household income, AJCC stage of disease, and cancer treatment (categorized as yes/no for receipt of surgery, radiotherapy, or chemotherapy). Additional models were adjusted for type of treating health facility and type of individual health insurance. The proportional hazards assumption was tested by examining parallelism in ln(-ln(survival)) versus ln(time) plots. No violations of this assumption were observed for HIV across any cancer site. However, violations were observed for cancer stage and treatment, requiring time-dependent adjustment for these 2 variables in regression models.

In a supplemental analysis, we examined logistic and Cox models for stage of disease and mortality outcomes, respectively, within patient groups aged <65 years stratified by receipt of specific types of health insurance: 1) private insurance; 2) Medicare; or 3) Medicaid.

RESULTS

We compared cancer stage at the time of presentation and mortality after cancer diagnosis in >6 million patients with cancer in the United States from the NCDB, including 14,453 PLWH who were diagnosed with cancer between 2004 and 2014 (Table 1). HIV-infected patients with cancer were younger, were more likely to be male and nonwhite, and had a lower median household income compared with HIV-uninfected patients with cancer ($P < .0001$). The most common cancer diagnoses in PLWH were lung cancer (29.1% of all cases), colorectal cancer (14.1%), and prostate cancer (10.5%), compared with cancers of the breast (22.8%), prostate (17.8%), and lung (17.7%) among HIV-uninfected patients, reflecting differences in the patient sex distribution by HIV status. We observed significant differences in the percentage of uninsured patients with cancer by HIV status (HIV-infected: 5.0% vs HIV-uninfected: 3.3%; $P < .0001$), with PLWH being approximately one-half as likely to report private health insurance (HIV-infected: 25.4% vs HIV-uninfected: 44.7%) and approximately 3 times more likely to be covered by Medicaid (HIV-infected: 17.9% vs HIV-uninfected: 5.9%). The likelihood of receiving cancer treatment and the type of health facility at which treatment was administered also differed by HIV status ($P < .0001$).

PLWH were more likely to be diagnosed with advanced-stage cancers of the oral cavity, liver, female breast, prostate, and thyroid and melanoma (P for trend <.05) (Table 2). After adjustment for both the type of treating health care facility and individual health insurance, statistically significant trends toward later-stage disease remained, with the association between HIV and stage IV disease (vs stage I) ranging from 1.24 (95% CI, 1.02-1.52) for liver cancer to 2.06 (95% CI, 1.70-2.50) for female breast cancer. It is interesting to note that HIV was associated with a marginally earlier stage of disease at the time of diagnosis for colorectal cancer (stage IV vs stage I: odds ratio [OR], 0.89 [95% CI, 0.78-1.02; P for trend = .03]) and a substantially earlier stage for anal cancer (OR, 0.54 [95% CI, 0.41-0.73; P for trend <.01]). After restricting analyses to patients aged <65 years and stratifying by receipt of either private insurance, Medicare, or Medicaid, results were largely consistent (see Supporting Table 1). The association between HIV and advanced-stage breast cancer was more pronounced among women with private insurance (OR, 2.22) or Medicare (OR, 2.27), both of which are groups assumed to have good access to care, compared with an OR of 0.77 in women with Medicaid. The association between HIV and advanced-stage cancers of the stomach and kidney was not statistically significant overall but was strongly positive among patients with Medicare (stomach: OR, 3.46 [95% CI, 1.67-7.48]; and kidney: 1.85 [95% CI, 1.09-3.15]).

Among patients with stage I to stage III disease, HIV was found to be significantly associated with elevated mortality after a cancer diagnosis for 13 of the 14 sites evaluated, even after adjustment for stage at diagnosis, first-course cancer treatment type of treating cancer facility, and type of individual health insurance (Table 3) (see Supporting Table 2). The strength of the association between HIV and overall mortality ranged from hazard ratios of 1.20 (95% CI, 1.14-1.26) for lung cancer to 1.85 (95% CI, 1.68-2.04), 1.85 (95% CI, 1.51-2.27), and 2.93 (95% CI, 2.08-4.13), respectively, for cancers of the female breast, cervix, and thyroid. The 5 cancers with the most pronounced HIV-associated elevations in mortality after diagnosis are illustrated in Figure 1 and included both virus-associated and non–virus-associated tumors. We also confirmed that PLWH experienced significantly elevated mortality even after including patients with metastatic (stage IV) disease (see Supporting Table 3).

DISCUSSION

The data from the current study regarding >6 million patients with cancer in the United States are consistent with PLWH experiencing a more aggressive disease

TABLE 1. Characteristics of Patients in the NCDB (2004 Through 2014) According to HIV Status

Demographic Factors	Total N = 6,382,579 No. (%)	HIV-Infected Patients N = 14,453 No. (%)	HIV-Uninfected Patients N = 6,368,126 No. (%)	Chi-square *P*
Sex				
Male	3,146,045 (49.3)	9296 (64.3)	3,136,749 (49.3)	<.0001
Female	3,236,534 (50.7)	5157 (35.7)	3,231,377 (50.7)	
Age at diagnosis, y				
18-44	543,310 (8.5)	1452 (10)	541,858 (8.5)	<.0001
45-54	1,075,558 (16.9)	3513 (24.3)	1,072,045 (16.8)	
55-64	1,733,796 (27.2)	3597 (24.9)	1,730,199 (27.2)	
≥65	3,029,915 (47.5)	5891 (40.8)	3,024,024 (47.5)	
Race/ethnicity				
White, non-Hispanic	4,726,015 (74.1)	7966 (55.1)	4,718,049 (74.1)	<.0001
Black	328,450 (5.1)	1054 (7.3)	327,396 (5.1)	
Hispanic	689,689 (10.8)	4533 (31.4)	685,156 (10.8)	
Other	206,283 (3.2)	177 (1.2)	206,106 (3.2)	
Missing data	432,142 (6.8)	723 (5)	431,419 (6.8)	
Y of cancer diagnosis				
2004-2006	1,628,351 (25.5)	5141 (35.6)	1,623,210 (25.5)	<.0001
2007-2010	2,366,096 (37.1)	5912 (40.9)	2,360,184 (37.1)	
2011-2014	2,388,132 (37.4)	3400 (23.5)	2,384,732 (37.4)	
Median income level				
<$38,000	1,120,358 (17.6)	4150 (28.7)	1,116,208 (17.5)	<.0001
$38,000-$47,999	1,466,892 (23)	3280 (22.7)	1,463,612 (23)	
$48,000-$62,999	1,676,914 (26.3)	3254 (22.5)	1,673,660 (26.3)	
≥$63,000	2,013,696 (31.5)	3444 (23.8)	2,010,252 (31.6)	
Missing data	104,719 (1.6)	325 (2.3)	104,394 (1.6)	
Cancer site				
Oral cavity/pharynx/larynx	289,643 (4.5)	939 (6.5)	288,704 (4.5)	<.0001
Stomach	106,060 (1.7)	290 (2)	105,770 (1.7)	
Colorectum	784,001 (12.3)	2034 (14.1)	781,967 (12.3)	
Anus	30,793 (0.5)	1052 (7.3)	29,741 (0.5)	
Liver	107,544 (1.7)	823 (5.7)	106,721 (1.7)	
Pancreas	211,219 (3.3)	498 (3.4)	210,721 (3.3)	
Lung	1,130,306 (17.7)	4201 (29.1)	1,126,105 (17.7)	
Melanoma	263,127 (4.1)	214 (1.5)	262,913 (4.1)	
Female breast	1,449,954 (22.7)	1197 (8.3)	1,448,757 (22.8)	
Cervix	95,222 (1.5)	330 (2.3)	94,892 (1.5)	
Prostate	1,136,297 (17.8)	1513 (10.5)	1,134,784 (17.8)	
Bladder	176,320 (2.8)	394 (2.7)	175,926 (2.8)	
Kidney	314,810 (4.9)	708 (4.9)	314,102 (4.9)	
Thyroid	287,283 (4.5)	260 (1.8)	287,023 (4.5)	
Individual insurance status				
Private	2,852,824 (44.7)	3667 (25.4)	2,849,157 (44.7)	<.0001
Medicaid	380,678 (6.0)	2587 (17.9)	378,091 (5.9)	
Medicare	2,770,671 (43.4)	7234 (50.0)	2,763,437 (43.5)	
Uninsured	211,643 (3.3)	717 (5.0)	210,926 (3.3)	
Government	34,223 (0.5)	72 (0.5)	34,151 (0.5)	
Missing data	132,540 (2.1)	176 (1.2)	132,364 (2.1)	
Type of treating health facility				
Community center	628,450 (9.8)	1410 (9.8)	627,040 (9.8)	<.0001
Comprehensive community center	2,712,165 (42.5)	5435 (37.6)	2,706,730 (42.5)	
Teaching/research institution	1,466,395 (23)	3833 (26.5)	1,462,562 (23)	
NCI network cancer center	731,239 (11.5)	1774 (12.3)	729,465 (11.5)	
Integrated network	649,528 (10.2)	1463 (10.1)	648,065 (10.2)	
Others/unknown	194,802 (3.1)	538 (3.7)	194,264 (3.1)	
Receipt of surgery, radiotherapy or chemotherapy				
Yes	5,758,785 (90.2)	11,598 (80.2)	5,747,187 (90.3)	<.0001
No	610,101 (9.6)	2802 (19.4)	607,299 (9.5)	
Unknown	13,693 (0.2)	53 (0.4)	13,640 (0.2)	

Abbreviations: NCDB, National Cancer Data Base; NCI, National Cancer Institute.

course for cancer: herein, we reported significant associations between HIV and both advanced stage of disease at the time of presentation and elevated mortality after a cancer diagnosis. Specifically, PLWH were significantly more likely to be diagnosed with advanced-stage cancers of the oral cavity, liver, female breast, prostate, and

TABLE 2. ORs and 95% CIs Describing the Association Between Patient HIV Status and AJCC Stage of Disease at the Time of Diagnosis

Cancer Site	Total Cases No. (%)	HIV-Infected Cases No. (%)	HIV-Uninfected Cases No. (%)	Model 1, Not Adjusted for Health Care Factors[a]	Model 2, Adjusted for Health Care Factors[b]
Oral cavity/pharynx/larynx					
Stage I	65,128 (22.5)	127 (13.5)	65,001 (22.5)	1	1
Stage II	38,100 (13.2)	108 (11.5)	37,992 (13.2)	1.32 (1.02-1.71)	1.24 (0.96-1.6)
Stage III	50,123 (17.3)	176 (18.7)	49,947 (17.3)	1.52 (1.21-1.91)	1.38 (1.1-1.74)
Stage IV	136,292 (47.1)	528 (56.2)	135,764 (47.0)	1.54 (1.27-1.88)	1.35 (1.1-1.64)
P for trend				**.0001**[c]	**.0134**
Stomach					
Stage I	28,157 (26.5)	76 (26.2)	28,081 (26.5)	1	1
Stage II	15,341 (14.5)	43 (14.8)	15,298 (14.5)	1.01 (0.69-1.47)	1.03 (0.71-1.5)
Stage III	15,783 (14.9)	39 (13.5)	15,744 (14.9)	0.83 (0.56-1.23)	0.85 (0.58-1.26)
Stage IV	46,779 (44.1)	132 (45.5)	46,647 (44.1)	0.95 (0.71-1.26)	0.94 (0.71-1.26)
P for trend				.7826	.7070
Colorectum					
Stage I	181,014 (23.1)	465 (22.9)	180,549 (23.1)	1	1
Stage II	208,371 (26.6)	616 (30.3)	207,755 (26.6)	1.16 (1.03-1.31)	1.13 (1-1.27)
Stage III	227,004 (29.0)	557 (27.4)	226,447 (29.0)	1 (0.88-1.13)	0.98 (0.87-1.11)
Stage IV	167,612 (21.4)	396 (19.5)	167,216 (21.4)	0.94 (0.82-1.08)	0.89 (0.78-1.02)
P for trend				.1559	**.0313**
Anus					
Stage I	6130 (19.9)	229 (21.8)	5901 (19.8)	1	1
Stage II	11,996 (39.0)	385 (36.6)	11,611 (39.0)	0.86 (0.72-1.02)	0.83 (0.7-0.99)
Stage III	10,064 (32.7)	369 (35.1)	9695 (32.6)	0.9 (0.76-1.08)	0.86 (0.72-1.03)
Stage IV	2603 (8.5)	69 (6.6)	2534 (8.5)	0.57 (0.43-0.76)	0.54 (0.41-0.73)
P for trend				**.0100**	**.0027**
Liver					
Stage I	38,333 (35.6)	242 (29.4)	38,091 (35.7)	1	1
Stage II	21,727 (20.2)	165 (20.0)	21,562 (20.2)	1.1 (0.9-1.35)	1.09 (0.89-1.33)
Stage III	27,884 (25.9)	246 (29.9)	27,638 (25.9)	1.27 (1.06-1.52)	1.31 (1.09-1.57)
Stage IV	19,600 (18.2)	170 (20.7)	19,430 (18.2)	1.19 (0.97-1.45)	1.24 (1.02-1.52)
P for trend				**.0309**	**.0084**
Pancreas					
Stage I	17,995 (8.5)	46 (9.2)	17,949 (8.5)	1	1
Stage II	62,661 (29.7)	142 (28.5)	62,519 (29.7)	0.84 (0.6-1.17)	0.84 (0.6-1.17)
Stage III	22,989 (10.9)	45 (9.0)	22,944 (10.9)	0.65 (0.43-0.99)	0.65 (0.43-0.98)
Stage IV	107,574 (50.9)	265 (53.2)	107,309 (50.9)	0.83 (0.6-1.13)	0.82 (0.6-1.13)
P for trend				.5813	.5703
Lung					
Stage I	238,623 (21.1)	790 (18.8)	237,833 (21.1)	1	1
Stage II	63,768 (5.6)	224 (5.3)	63,544 (5.6)	0.91 (0.79-1.06)	0.92 (0.79-1.07)
Stage III	293,173 (25.9)	1090 (25.9)	292,083 (25.9)	0.94 (0.85-1.03)	0.93 (0.84-1.01)
Stage IV	534,742 (47.3)	2097 (49.9)	532,645 (47.3)	0.97 (0.89-1.05)	0.97 (0.89-1.05)
P for trend				.8945	.9718
Melanoma					
Stage I	172,448 (65.5)	110 (51.4)	172,338 (65.5)	1	1
Stage II	42,586 (16.2)	35 (16.4)	42,551 (16.2)	1.12 (0.77-1.65)	1.05 (0.71-1.54)
Stage III	32,356 (12.3)	38 (17.8)	32,318 (12.3)	1.52 (1.05-2.21)	1.41 (0.97-2.06)
Stage IV	15,737 (6.0)	31 (14.5)	15,706 (6.0)	2.37 (1.58-3.56)	1.96 (1.3-2.97)
P for trend				**<.0001**	**.0022**
Female breast					
Stage I	692,293 (47.8)	453 (37.8)	691,840 (47.8)	1	1
Stage II	502,964 (34.7)	419 (35)	502,545 (34.7)	1.2 (1.05-1.37)	1.16 (1.02-1.33)
Stage III	179,480 (12.4)	185 (15.5)	179,295 (12.4)	1.36 (1.14-1.62)	1.26 (1.06-1.5)
Stage IV	75,217 (5.2)	140 (11.7)	75,077 (5.2)	2.36 (1.95-2.85)	2.06 (1.70-2.50)
P for trend				**<.0001**	**<.0001**
Cervix					
Stage I	45,105 (47.4)	146 (44.2)	44,959 (47.4)	1	1
Stage II	14,506 (15.2)	53 (16.1)	14,453 (15.2)	1.2 (0.87-1.65)	1.05 (0.76-1.45)
Stage III	22,528 (23.7)	78 (23.6)	22,450 (23.7)	1.05 (0.79-1.38)	0.92 (0.69-1.22)
Stage IV	13,083 (13.7)	53 (16.1)	13,030 (13.7)	1.42 (1.03-1.96)	1.22 (0.88-1.69)
P for trend				.0866	.5754
Prostate					
Stage I/II[d]	939,405 (82.7)	1190 (78.7)	938,215 (82.7)	1	1
Stage III	115,700 (10.2)	135 (8.9)	115,565 (10.2)	0.97 (0.82-1.17)	0.96 (0.8-1.15)
Stage IV	81,192 (7.1)	188 (12.4)	81,004 (7.1)	1.81 (1.55-2.12)	1.57 (1.34-1.83)
P for trend				**<.0001**	**<.0001**

TABLE 2. *Continued*

Cancer Site	Total Cases No. (%)	HIV-Infected Cases No. (%)	HIV-Uninfected Cases No. (%)	Model 1, Not Adjusted for Health Care Factors[a]	Model 2, Adjusted for Health Care Factors[b]
Bladder					
Stage I	81,514 (46.2)	170 (43.1)	81,344 (46.2)	1	1
Stage II	46,726 (26.5)	118 (30)	46,608 (26.5)	1.2 (0.95-1.52)	1.19 (0.94-1.5)
Stage III	18,135 (10.3)	36 (9.1)	18,099 (10.3)	0.9 (0.63-1.29)	0.89 (0.62-1.28)
Stage IV	29,945 (17.0)	70 (17.8)	29,875 (17.0)	1.04 (0.78-1.38)	1 (0.75-1.33)
P for trend				.7419	.8901
Kidney					
Stage I	185,725 (59.0)	412 (58.2)	185,313 (59.0)	1	1
Stage II	28,666 (9.1)	56 (7.9)	28,610 (9.1)	0.81 (0.61-1.08)	0.84 (0.64-1.11)
Stage III	46,784 (14.9)	105 (14.8)	46,679 (14.9)	1.05 (0.85-1.31)	1.07 (0.86-1.33)
Stage IV	53,635 (17.0)	135 (19.1)	53,500 (17.0)	1.09 (0.89-1.32)	1.06 (0.87-1.3)
P for trend				.6677	.6752
Thyroid					
Stage I	207,173 (72.1)	149 (57.3)	207,024 (72.1)	1	1
Stage II	23,217 (8.1)	23 (8.8)	23,194 (8.1)	0.94 (0.59-1.48)	0.92 (0.58-1.45)
Stage III	35,457 (12.3)	42 (16.2)	35,415 (12.3)	1.23 (0.85-1.78)	1.15 (0.8-1.67)
Stage IV	21,436 (7.5)	46 (17.7)	21,390 (7.5)	1.95 (1.36-2.81)	1.67 (1.16-2.41)
P for trend				**.0007**	**.0072**

Abbreviations: AJCC, American Joint Committee on Cancer; OR, odds ratio.
[a]Model 1 was adjusted for age, sex, race, calendar year of cancer diagnosis, and median household income (by zip code).
[b]Model 2 was adjusted for age, sex, race, calendar year of cancer diagnosis, median household income (by zip code), patient-reported individual health insurance, and type of treating cancer facility.
[c]Bold text indicates statistical significance for the *P* for trend test describing the likelihood of diagnosis with more advanced stages of disease by HIV status.
[d]Individual AJCC stage groupings with <10 patients were collapsed into categories to provide more stable effect estimates (eg, patients with stage I and stage II prostate cancer were combined into stage I/II disease).

thyroid and melanoma. Furthermore, HIV was associated with elevated mortality after a cancer diagnosis for 13 of the 14 cancer sites evaluated, including an almost doubling and tripling of mortality for female breast and thyroid cancers, respectively. The persistence of these associations after adjustment for factors related to the receipt of health care provides support for a biological link between HIV-related immunosuppression and cancer progression.

To the best of our knowledge, only 1 prior study to date broadly examined cancer stage in PLWH; in that study, HIV was found to be associated with a more advanced stage of disease in patients with cancers of the lung, breast, prostate, and bladder and melanoma.[17] However, that study did not have information regarding the type of care received by HIV status.[17] To mitigate this fact, the authors compared their results with those observed among recipients of solid organ transplants, an immunosuppressed patient group that, unlike PLWH, has increased use of health care. Consistent results for more advanced-stage diagnoses of bladder cancer and melanoma suggested a possible biological role for immunosuppression in the progression of these cancers. We believe the current study was unique in that the availability of health insurance information in the NCDB enabled us to more directly address potential nonbiological explanations for later-stage cancer diagnoses in PLWH. We confirmed prior associations between HIV and later-stage breast cancer, prostate cancer, and melanoma.[17] In addition, herein we reported associations between HIV and advanced-stage cancers of the oral cavity, liver, and thyroid. Because these associations were independent of the type of health insurance a patient reported, it appears that access to health care is not the sole explanation for the stage shifts.

The results of the current study do highlight one notable exception: PLWH were substantially more likely to be diagnosed with less advanced anal cancers compared with their HIV-uninfected counterparts. This potentially represents an example of increased health care being directed toward the HIV-infected population, a distinct possibility given the ongoing targeting of anal cancer screening procedures to HIV-infected men who have sex with men.[22] It is important to note that although these immunosuppressed patients were more likely to be diagnosed with less advanced disease, their stage-adjusted mortality was higher than that of HIV-uninfected patients. Mortality after an anal cancer diagnosis was found to be approximately 34% higher in PLWH compared with HIV-uninfected patients diagnosed with the same stage of disease in the current study.

The association between HIV and elevated mortality after a cancer diagnosis was observed for patients with stage I to stage III tumors regardless of

TABLE 3. HRs and 95% CIs Describing the Association Between Patient HIV Status and Mortality After Cancer Diagnosis

Cancer Site	Total Cases	Deaths (% of Cases)	Model 1, Not Adjusted for Health Care Factors[a]	Model 2, Adjusted for Health Care Factors[b]
Oral cavity/pharynx/larynx				
HIV-infected	353	194 (55.0%)	1.89 (1.64-2.18)	1.66 (1.44-1.92)
HIV-uninfected	123,760	44,303 (35.8%)	1	1
Stomach				
HIV-infected	141	106 (75.2%)	1.25 (1.03-1.52)	1.20 (0.98-1.45)
HIV-uninfected	47,263	28,895 (61.1%)	1	1
Colorectum				
HIV-infected	1524	903 (59.3%)	1.65 (1.54-1.76)	1.58 (1.48-1.69)
HIV-uninfected	505,650	181,240 (35.8%)	1	1
Anus				
HIV-infected	764	319 (41.8%)	1.56 (1.38-1.76)	1.34 (1.19-1.52)
HIV-uninfected	21,032	6601 (31.4%)	1	1
Liver				
HIV-infected	515	422 (81.9%)	1.32 (1.19-1.46)	1.29 (1.16-1.42)
HIV-uninfected	65,652	46,977 (71.6%)	1	1
Pancreas				
HIV-infected	212	198 (93.4%)	1.37 (1.19-1.59)	1.34 (1.16-1.54)
HIV-uninfected	81,115	67,982 (83.8%)	1	1
Lung				
HIV-infected	1908	1547 (81.1%)	1.24 (1.18-1.3)	1.20 (1.14-1.26)
HIV-uninfected	483,000	340,444 (70.5%)	1	1
Melanoma				
HIV-infected	145	57 (39.3%)	1.79 (1.38-2.32)	1.65 (1.27-2.14)
HIV-uninfected	194,402	37,221 (19.1%)	1	1
Female breast				
HIV-infected	957	399 (41.7%)	1.98 (1.80-2.19)	1.85 (1.68-2.04)
HIV-uninfected	1,099,101	173,881 (15.8%)	1	1
Cervix				
HIV-infected	218	95 (43.6%)	2.06 (1.68-2.52)	1.85 (1.51-2.27)
HIV-uninfected	67,181	17,506 (26.1%)	1	1
Prostate				
HIV-infected	1170	236 (20.2%)	1.65 (1.46-1.88)	1.56 (1.37-1.77)
HIV-uninfected	901,852	112,889 (12.5%)	1	1
Bladder				
HIV-infected	302	217 (71.9%)	1.71 (1.50-1.96)	1.66 (1.45-1.9)
HIV-uninfected	117,311	57,533 (49.0%)	1	1
Kidney				
HIV-infected	514	204 (39.7%)	1.52 (1.32-1.75)	1.41 (1.22-1.62)
HIV-uninfected	205,898	45,884 (22.3%)	1	1
Thyroid				
HIV-infected	190	33 (17.4%)	3.10 (2.20-4.37)	2.93 (2.08-4.13)
HIV-uninfected	206,656	7841 (3.8%)	1	1

Abbreviation: HR, hazard ratio.
[a]Model 1 was adjusted for age, sex, race, calendar year of cancer diagnosis, median household income (by zip code), American Joint Committee on Cancer stage of disease, and treatment.
[b]Model 2 was adjusted for model 1 plus the type of individual health insurance and treating cancer facility.

their initiating etiology. Elevations in mortality among patients with cancer ranged from 20% (lung cancer) to approximately 3-fold (thyroid cancer) in PLWH, with the largest HIV-related differences observed for cancers with a generally good prognosis (eg, breast and thyroid cancers).[23] These data are consistent with prior work demonstrating higher mortality rates among patients with cancer within the setting of HIV.[18,24-26] However, this study not only accounted for clinically important prognostic factors such as cancer stage and treatment, but also demonstrated higher mortality in HIV-infected patients with cancer after accounting for the type of treating health facility (quality of cancer care) and individual health insurance (access to care). Furthermore, the NCDB includes only patients with cancer who at least initiated cancer care, as opposed to our prior study that included diagnoses of cancer among all PLWH, regardless of health care use.[18]

Ultimately, patients with cancer with the same stage of disease at the time of presentation, the same initial treatment modality, reporting similar health insurance, and receiving cancer care at the same type of health care facility still died more often if they were infected with HIV at the time of their cancer diagnosis. A biological explanation

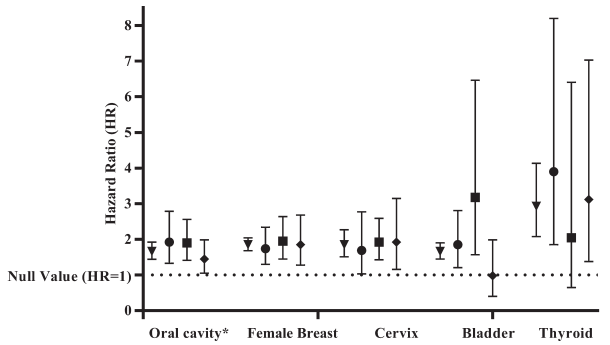

Figure 1. Hazard ratios (HRs) illustrating the association between HIV status and elevated mortality after a cancer diagnosis for the 5 cancer sites with the strongest effect estimates, according to the type of individual health insurance reported. (Triangle indicates original HR estimate; circle, estimate for those with private insurance; square, estimate for those with Medicaid; diamond, estimate for those with Medicare). *Oral cavity includes the oral cavity, pharynx, and/or larynx.

for this persistent effect of immunosuppression on outcomes in patients with cancer is plausible when considered alongside data suggesting that immunosuppressed solid organ transplant recipients also experience elevated mortality after a cancer diagnosis,[27] recent advances in cancer survival associated with immune-boosting therapies,[28-30] and data suggesting that additional cancer-specific outcomes (ie, disease recurrence after successful first-course treatment) are poorer in the presence of HIV.[31] However, it must be acknowledged that this evaluation focused on overall mortality as the clinically relevant outcome rather than death due specifically to cancer. It is possible that PLWH in the current study died more often due in part to a higher risk of additional causes of death, including AIDS and other HIV-associated comorbidities.

The current study is notable not only for the size and national scope of the NCDB but also because to the best of our knowledge prior studies have not been able to broadly examine the possibility that variations in health care could offer a nonbiological explanation for the more advanced-stage cancer and elevated mortality after a cancer diagnosis noted among PLWH. Instead of proving a nonbiological explanation for the link between HIV and tumor aggressiveness, our data suggest that biology could underlie this association.

Certain limitations of the current study should be noted. First, we were unable to rule out the possibility of HIV-related differences in access to health care that we were not able to account for in our models. For example, our classification of insurance into large groupings (eg, private insurance) may have failed to adequately adjust for variations according to insurance provider or coverage levels. Simple adjustment for receipt of health insurance also likely did not capture variations in the use of health services (ie, having and using insurance are not equivalent). Additional misclassification also may have existed for our exposure; hospital discharge diagnoses likely underascertain HIV status. As noted above, our evaluation of overall mortality after a cancer diagnosis was not able to capture potentially important HIV-related differences in cancer-specific mortality. Finally, we were not able to address the association between clinical measures of immunosuppression (eg, CD4 count) or HIV treatment (eg, antiretroviral therapy) and outcomes because the NCDB does not collect this information. Future studies that include clinical HIV data should evaluate these more refined metrics of patient immune status.

The results of the current study of >6 million patients with cancer in the United States demonstrated that those infected with HIV were more likely to be diagnosed with advanced-stage cancers of the oral cavity, liver, female breast, prostate, and thyroid and melanoma. PLWH who were diagnosed with stage I to stage III cancer also experienced elevated mortality after diagnosis across a range of tumor etiologies. These associations persisted even after accounting for HIV-related differences with regard to the type of treating cancer facility and patient-reported individual health insurance. Although the possibility remains that the current study findings could be explained partly by unmeasured differences in health care use, differences in applied cancer treatment, or mortality from noncancer comorbidities, the results support a possible biological association between HIV and tumor behavior.

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