Short Communication: Differences in 5-Year Survival After Cancer Diagnosis Between HIV Clinic Enrollees and the General U.S. Population

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Abstract

A total of 236 people with HIV (PWH) with cancer diagnosed between 1997 and 2014 in the Johns Hopkins HIV Clinical Cohort (JHHCC) were compared with a sample from NCI's Surveillance, Epidemiology, and End Results (SEER) Program, presumed to be HIV negative. Using G-computation with random survival forest methods, we estimated 5-year restricted mean survival time (RMST) differences by HIV status. Sensitivity analyses were performed among non-AIDS defining cancers, males, females, and stratifying PWH by $CD4 \leq 200$ or >200 cells/mm³ at cancer diagnosis. PWH with $CD4 \leq 200$ cells/mm³ had decreased survival compared with those in SEER (−7 months; 95% CI = −13 to −2). Women with HIV and $CD4 \leq 200$ cells/mm³ at cancer diagnosis had lower survival than SEER women (−10 months; 95% CI = −18 to −2). In the total population, there was no significant difference in 5-year RMST; however, women with HIV and low CD4 had higher mortality despite accounting for stage at diagnosis and first course of cancer treatment.

Keywords: HIV infection, cancer, cancer survival, CD4

PEOPLE WITH HIV (PWH) may experience higher rates of mortality after cancer diagnosis than the general U.S. population.^{1,2} Factors such as immune suppression, smoking, viral coinfections, and lower access to care likely play a role in survival differences by HIV status.³ Because PWH may be diagnosed at more advanced cancer stages and receive lower rates of cancer treatment,^{4,5} we sought to isolate whether mortality differences existed accounting for these factors and to what extent they varied by immune status. In this study, we examine the effect of HIV on 5-year restricted mean survival time (RMST) after a first incident cancer diagnosis using data from an urban HIV clinic and individuals in the general U.S. population with the same cancers in the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER). We conducted subanalyses among non-AIDS defining cancers (NADC), by sex, and by CD4 cell count at cancer diagnosis as a measure of HIV-related immune suppression.

All incident first cancer cases among individuals enrolled in the Johns Hopkins HIV Clinical Cohort (JHHCC) between January 1, 1997, and September 30, 2014, were identified ($N=382$), and 77% of all cases were linked to the Maryland

Cancer Registry* to obtain information on validated cancer type, stage at diagnosis, and first course of treatment. After excluding all Kaposi's sarcoma, nonspecific cancer types (e.g., skin), and cancers with no staging information in SEER, a total of 236 cancers among PWH in the JHHCC were in the study sample. All incident first cancer cases of the same type as the JHHCC among individuals aged 21–80 years were identified in the SEER registries between 2000 and 2014. Cancer cases in SEER are presumed to be representative of cancer cases among the general U.S. population,⁶ and the vast majority of these cases are thought to be among HIV negative individuals. We restricted our analysis of SEER data to first cancers diagnosed in persons aged 21–80 years with a cancer type in JHHCC data.

We examined differences in the 5-year RMST to all-cause mortality using G-computation with random survival forest methods.^{7,8} G-computation is equivalent to direct standardization.⁹ In this case, we standardized the covariates to

*Cancer incidence data were provided by the Maryland Cancer Registry, Center for Cancer Prevention and Control, Maryland Department of Health, Baltimore, Maryland. https://phpa.health.maryland.gov/cancer/Pages/mcr_home.aspx

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match the distribution of those with HIV based on the random survival forest models, which were developed separately by HIV status. The model covariates were cancer type, age, sex, race, year of diagnosis, stage at diagnosis, any chemotherapy, any radiation, and any surgery. Stage at diagnosis was categorized into localized, regional, distant, or unstaged. Separate random forest models were constructed within for each of the subanalyses (NADC, males, and females), and by baseline CD4 ≤ 200 or >200 cells/mm³ overall and among all subanalyses. A total of 210 (89%) PWH in JHHCC had information on baseline CD4. Results stratified by baseline CD4 also included CD4 at cancer diagnosis in the random forest models for PWH in JHHCC. The random survival forest models were estimated using a 1% sample of the SEER data (~18,900 cases) to reduce computation time. The 95% confidence intervals (CIs) used the bootstrap variance of the effect estimates based on 200 iterations. Each iteration of the bootstrap took a new random sample of the SEER data and re-estimated the random survival forest models. All analyses were performed in R,¹⁰ including the randomForestSRC⁸ package.

Among the 236 cancers in PWH enrolled in the JHHCC, 163 were among males (69%) and 73 were among females (31%). There were a total of 183 NADCs. The most common cancer types included 53 non-Hodgkin's lymphomas (NHLs), 42 lung cancers, 23 liver cancers, 18 Hodgkin's lymphomas, 18 prostate cancers, and 16 breast cancers. Median age was 50 years (interquartile range 44–56). Among females in the JHHCC, breast cancer ($N=16$) and lung cancer ($N=16$) were the most common diagnoses, whereas NHL ($N=41$) and lung cancer ($N=26$) were the most common diagnoses among males. The population was 78% non-Hispanic black and 39% reported injection drug use as their likely HIV acquisition risk factor. A total of 88% of PWH with cancer were on anti-retroviral therapy at the time of cancer diagnosis. Results comparing all-cause mortality after cancer diagnosis by HIV are presented in Table 1. Overall, the 5-year RMST for PWH was 32 months (95% CI=30–35), as compared with 34 months for people without HIV (95% CI=34–35). This did not represent a significant difference in survival by HIV status

(RMST difference=–2 months; 95% CI=–4 to 1). PWH with baseline CD4 ≤ 200 cells/mm³ had on average a 7-month shorter survival after cancer diagnosis than those without HIV (95% CI=–13 to –2). No differences in survival were observed among those with NADC and among men, even among when restricted to PWH with CD4 ≤ 200 cells/mm³. Women with HIV and CD4 ≤ 200 cells/mm³ had on average a 10-month shorter survival than women without HIV (95% CI=–18 to –2). A sensitivity analysis in the total population found that removing stage at diagnosis and cancer treatment from the model resulted in significantly lower survival among PWH (RMST difference=–4 months; 95% CI=–7 to –1). These results were consistent across all strata.

Overall, we found no differences in survival by HIV status after accounting for cancer type, stage at diagnosis, cancer treatment, and demographic factors. This differs from prior studies that found higher overall and cancer-specific mortality among PWH than those without HIV.^{1,2} However, we found lower survival for PWH at lower CD4 levels, particularly among women. It is possible that immune suppression plays a role in the progression of cancer among PWH or that AIDS progression might explain differences in survival for those with lower CD4.³ Among the 138 deaths that occurred among PWH in the JHHCC within 5 years of cancer diagnosis, 74% were attributed to cancer, 6% were attributed to HIV, and 20% were attributed to other causes. More evidence on the tolerability and efficacy of treatment among PWH, particular among women and those with low CD4 cell counts, is needed. We also found lower survival among PWH when the models that did not include stage at diagnosis and cancer treatment, suggesting that differences in stage at diagnosis and cancer treatment may explain previously observed survival differences after cancer diagnosis by HIV status.^{4,5} Information on predictors of earlier detection of cancers among PWH would improve prognosis for these individuals.

We were limited by relatively small number of cancer cases among PWH from a single institution, restricting the generalizability of our findings and precluding analyses of particular cancer types. A replication of this analysis among individual cancer types with sufficient sample size would

TABLE 1. THE 5-YEAR RESTRICTED MEAN SURVIVAL TIME STRATIFIED BY HIV STATUS AND RESTRICTED MEAN SURVIVAL TIME DIFFERENCE (HIV–NON-HIV) IN MONTHS AFTER DIAGNOSIS WITH AN INCIDENT PRIMARY CANCER

CD4 strata (cells/mm ³)		HIV sample size, N	HIV RMST months (95% CI)	Non-HIV RMST months (95% CI)	RMST difference months (95% CI) ^a
Total	All	236	32 (30 to 35)	34 (34 to 35)	–2 (–4 to 1)
	CD4 ≤ 200	68	27 (22 to 32)	34 (31 to 37)	–7 (–13 to –2)
	CD4 > 200	142	36 (32 to 40)	34 (32 to 37)	2 (–2 to 5)
NADC	All	183	31 (29 to 36)	30 (33 to 38)	1 (–2 to 4)
	CD4 ≤ 200	42	29 (24 to 34)	30 (26 to 34)	–1 (–6 to 4)
	CD4 > 200	122	34 (30 to 38)	33 (31 to 36)	1 (–2 to 4)
Men	All	163	32 (29 to 35)	33 (32 to 34)	–1 (–4 to 3)
	CD4 ≤ 200	47	28 (22 to 34)	32 (28 to 36)	–4 (–10 to 3)
	CD4 > 200	94	34 (29 to 39)	31 (28 to 34)	3 (–1 to 7)
Women	All	73	30 (26 to 35)	35 (34 to 36)	–4 (–9 to 0)
	CD4 ≤ 200	21	28 (20 to 36)	38 (32 to 43)	–10 (–18 to –2)
	CD4 > 200	48	37 (31 to 43)	40 (36 to 44)	–3 (–9 to 3)

Models adjusted for age, sex, race, year of diagnosis, cancer type, stage at diagnosis, receipt of chemotherapy, receipt of radiation, and receipt of surgery. CD4 stratified models are adjusted for baseline CD4.

^aBold text represents RMST differences with a 95% CI that does not include 0.

CI, confidence interval; NADC, non-AIDS defining cancers; RMST, restricted mean survival time.

allow further assessment of any heterogeneity in the effect of HIV on stage, treatment, and survival by cancer type. There are also limitations associated with comparing PWH in clinical care with the general population in SEER, including the fact that access to care may be lower among the general population since those in the JHHCC are by definition linked to care. This may reflect differences in preventative care and cancer screenings, as well as health-seeking behavioral differences. Strengths of our analysis included the use availability of cancer staging and treatment data among a diverse cohort of PWH, as well as information on CD4 cell count at cancer diagnosis. The 5-year RMST for PWH with CD4 > 200 cells/mm³ is reassuring and reinforces the need for earlier HIV diagnosis and improved antiretroviral therapy adherence to maximize CD4.

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Author Disclosure Statement

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