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A comparison of cancer stage at diagnosis and treatment initiation between enrollees in an urban HIV clinic and SEER

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Abstract

Purpose—A comparison of stage at cancer diagnosis and cancer treatment rates between people with HIV (PWH) and the general US population is needed to identify any disparities by HIV status.

Methods—We compared 236 PWH in clinical care diagnosed with cancer from 1997 to 2014 to a sample from NCI's Surveillance, Epidemiology and End Results (SEER) Program, presumed to be HIV negative. We performed G-computation using random forest methods to estimate stage and treatment percent differences (PD) by HIV. We conducted sensitivity analyses among non-AIDS-defining cancers (NADC), by sex and by CD4 ≤ 200 or > 200 cells/mm^3.

Results—PWH were less likely to be diagnosed at localized stage (PD = − 16%; 95% CI − 21, − 11) and more likely to be diagnosed at regional stage (PD = 14%; 95% CI 8, 19) than those in SEER. Cancer treatment rates were 13% lower among PWH as compared to SEER (95% CI − 18, − 8). The difference in percent receiving cancer treatment was more pronounced for those with lower CD4 at cancer diagnosis (PD −15%; 95% CI − 27, − 6). Lower treatment rates were observed among NADC, males, and women with CD4 ≤ 200.

Conclusion—Cancer care for PWH could be improved by diagnosis at earlier stages and increasing rates of cancer treatment.

Keywords

HIV infection; Cancer; Cancer stage; Cancer treatment; CD4

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Introduction

Cancer is a leading cause of morbidity and mortality among people with HIV (PWH) [1–3]. There is some evidence, although inconsistent, that PWH are diagnosed at more advanced stages of cancer [4, 5] and have lower rates of cancer treatment [6, 7]. Several factors may affect cancer treatment and outcomes in PWH compared to the general population. In particular, immunosuppression from HIV could result in the development of more aggressive cancers and may reduce tolerability of treatment or physician willingness to provide cancer treatment to PWH [4, 6]. In addition, PWH also experience higher rates of other risk factors, such as smoking and viral co-infections, that may affect cancer stage at presentation, treatment, and mortality [8–11]. Barriers in access to and engagement in care also play an important role in cancer outcomes among PWH [10, 11]. In this study, we compare stage at cancer diagnosis and initial cancer treatment rates between PWH engaged in clinical HIV care and individuals in the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER). SEER is representative of cancer cases among the general US population [12] and the vast majority are HIV negative [13–15]. We hypothesized that PWH would be diagnosed with a more advanced stage cancer [4] and would receive cancer treatment at lower rates [6, 7] than the general US population.

Methods

Data sources

We identified 382 incident, first cancer cases among PWH enrolled in the Johns Hopkins HIV Clinical Cohort (JHHCC) between 1 January 1997 and 30 September 2014 using a protocol developed by the Centers for AIDS Research Network of Integrated Clinical Systems [16]. Of the 382 total cases, 296 (77%) were linked to stage and treatment data in Maryland Cancer Registry (MCR).[1] We excluded all Kaposi's sarcoma cases, non-specific cancer types (e.g., skin cancers), and cancers with limited staging information in SEER (e.g., oral/pharynx), resulting in 236 cancers among PWH. A total of 1,756,229 incident, first cancers that matched the cancer types found in the JHHCC and had non-missing stage, were identified among persons aged 21–80 reported to SEER registries between 2000 and 2014.

Statistical analysis

Stage at diagnosis was categorized into localized, regional, distant, or unstaged based on the SEER Summary Stage 2000 classification [17]. Cancer treatment was defined as any chemotherapy, any radiation, and/or any surgery for the first course of treatment. We used G-computation to account for the differences in the covariate distribution by HIV status [18, 19], which is comparable to direct standardization where the standard population is PWH diagnosed with an incident, first cancer who are enrolled in the JHHCC [18, 20]. We fitted random forest models [21] for the outcome of interest separately for those with HIV (JHHCC) and for those without HIV (SEER) [19]. We included the following covariates in the random forest models for stage at diagnosis: cancer type, age, sex, race, and year of

[1]Cancer incidence data were provided by the Maryland Cancer Registry, Center for Cancer Prevention and Control, Maryland Department of Health, 201 W. Preston Street, Room 400, Baltimore, MD 21201, USA, https://phpa.health.maryland.gov/cancer/Pages/mcr_home.aspx, 410-767-4055.

diagnosis. The cancer treatment random forest models included cancer type, age, sex, race, year, and stage at diagnosis. Random forest is an ensemble machine learning algorithm formed by averaging tree-based learners (e.g., recursive partitioning). Random forest creates an ensemble learner by taking a random sample with replacement of the data and restricting the classification variables to a random subset of the total covariates as a way to introduce sufficient variation in each tree, allowing for the model to learn from each additional tree that is added to the forest until the point of diminishing return [21]. We then predicted the potential outcomes with and without HIV infection. The estimated effect of HIV infection is the average difference in the predicted potential outcomes. The results are presented as percent differences (PD). We repeated the analyses for each outcome among several subgroups, including those diagnosed with a nonAIDS-defining cancer (NADC) (N = 183 in JHHCC), males (N = 163 in JHHCC), and females (N = 73 in JHHCC). Analyses restricted to males or females excluded sex from the covariates. Due to large computational time, we estimated the random forest models using a 25% random sample of the SEER data (439,057 cases). We obtained all 95% confidence intervals (CI) using the bootstrap variance of the effect estimates based on 200 iterations. The bootstrap included a random sampling procedure and estimated the random forest models in each iteration. To address potential variation in the results by cancer type, we present forest plots of the estimated differences by HIV status in stage at diagnosis and percent receiving initial cancer treatment in the supplemental materials (Supplemental Figs. 1–4). All analyses were performed in R [22], including the randomForest [23] package.

Results

Among the 236 PWH in the JHHCC, 163 (69%) were male and 184 (78%) were non-Hispanic black. Their median age was 50 years (IQR 44–56). Common cancer types in the JHHCC include non-Hodgkin's lymphoma (NHL) (N = 53, 23%), lung cancer (N = 42, 18%), liver cancer (N = 23, 10%), Hodgkin lymphoma (N = 18, 8%), prostate cancer (N = 18, 8%), breast cancer (N = 16, 7%), and anal cancer (N = 15, 6%). Refer to the supplemental materials for a table with a full list of the cancer types in the JHHCC and the 25% SEER sample, as well as information on the unadjusted distributions of stage at diagnosis.

The probability of being diagnosed at each stage shown in percentages are provided for all cancers, all NADC, males, and females by HIV status and are presented in Fig. 1. These results can be interpreted as what the stage distribution is for PWH and what would be the stage distribution had those individuals not had HIV, adjusting for differences in cancer type, age, sex, race, and year of diagnosis. Cancer cases were less likely to be diagnosed as localized and more likely to be diagnosed as regional, if persons had HIV. Similar rates of diagnosis at distant stages were observed by HIV status. Among all cancers, 30% of individuals with HIV were diagnosed at a localized stage as compared to 46% of individuals without HIV, resulting in a 16% lower probability among PWH (95% CI − 22, − 10). A total of 19% of PWH were diagnosed at a regional stage as compared to 5% of those without HIV, yielding a 14% difference (95% CI 8, 19). Rates of diagnosis at a distant stage were similar with 47% of PWH as compared to 48% of those without HIV, yielding a − 2% percent difference (PD) (95% CI − 6, 5). Those with HIV were more likely to be unstaged

(PD = 3%; 95% CI 1, 6). The results are similar when the data are restricted to NADC and males. Among females, PWH were more likely to be diagnosed at a regional stage (PD = 13%; 95% CI 1, 26) but had similar rates at localized and distant stages. Unstaged cancers were excluded from the male and female models due to small sample size. In the sensitivity analyses, the results were fairly consistent across cancer types; however, lung cancer appeared to be more localized among those with HIV (Supplemental Fig. 1).

Probabilities of initial cancer treatment, presented as percentages in Table 1, are similarly lower among PWH than what we would have expected had they not had HIV. High rates of cancer treatment are expected based on data from SEER; however, among all cancers, 82% of PWH receive any initial cancer treatment as compared to 94% of those without HIV (PD = − 13%; 95% CI − 18, − 8), accounting for differences in cancer type, age, sex, race, year of diagnosis, and stage at diagnosis. There is a larger difference in initial cancer treatment for all cancers among PWH with CD4 ≤ 200 as compared to had they been HIV negative with a PD of − 15% (95% CI − 27, − 6); however, PWH with CD4 > 200 were also less likely to receive cancer treatment (PD = − 9; 95% CI − 14, − 2). Similar results are seen when restricting the analysis to NADC and males. Differences in rates of treatment were only observed for women with HIV and CD4 ≤ 200. This difference is pronounced, although there is significant variability in the estimate (PD = − 20%; 95% CI − 42, − 4). When stratified by cancer type, differences in treatment probability appeared consistent across types (Supplemental Fig. 4).

Discussion

We compared cancer stage at diagnosis and percent receiving any initial cancer treatment between PWH enrolled in HIV care (in the JHHCC) and the outcomes that we would expect had those individuals not had HIV, using the SEER data. Prior studies that have found PWH present at a later stage than those without HIV [4, 5, 24]. In this study, we found PWH were less likely to be diagnosed at a local stage and more likely to be diagnosed at a regional stage than had they not had HIV infection. The proportion of individuals diagnosed at a distant stage were similar by HIV status. To address this difference in stage at diagnosis by HIV status, more evidence on the benefits and harms of enhanced monitoring or early detection of cancer among PWH are needed (Table 1).

The percent of individuals receiving any initial cancer treatment was lower among people with HIV. This result echoes prior studies that have found lower cancer treatment rates for PWH [6, 7]. In contrast, a few prior studies have found no disparities in cancer treatment rates by HIV among those enrolled in managed care organizations [25, 26]. Our analysis was restricted o persons with HIV in continuity care, albeit with varying rates of engagement in care over time; however, we were limited our ability to study the role that access to care may play in disparities observed elsewhere. Yet we still found evidence of lower treatment, suggesting that poor retention in care or cancer treatment tolerability issues may impact cancer treatment uptake in this population. More evidence on the tolerability and efficacy of cancer treatment among PWH, particular among women and those with low CD4 cell counts, is needed [16].

Our sample of cancer cases among PWH came from a single institution, limiting the generalizability of our findings and precluding analyses of particular cancer types. It is important to note that our population is not representative of all PWH with cancer in the US, as it comprises individuals linked to clinical care. We are also comparing cancer outcomes with a sample of the general US population, who may or may not have had similar access to healthcare. We also had relatively limited information on cancer treatment. Our analyses focused on receipt of any initial cancer treatment and could not delineate whether the treatments were appropriate based on the guidelines and stage at diagnosis. Based on prior knowledge about lower treatment rates and issues with tolerability [6, 7], it is possible that PWH receiving initial treatment may not have received guideline appropriate treatment and then our results would be biased toward the null.

Another limitation of our analysis was the small sample size, which required an aggregation of the results across all cancer types. It is possible that the results are heavily influenced by the most common cancers found in the JHHCC, and this approach does not allow for an examination of heterogeneity by cancer type. We attempted to address these limitations with sensitivity analyses. First, we examined only those with NADCs, given that AIDS-defining cancers, particularly NHL, have known differences in subtype distributions by HIV status [27]. However, the NADC results were fairly consistent with the results among all cancers. Secondly, though underpowered, we presented results of the main analyses stratified by cancer type for the most common cancers to partially address this concern. A replication of this analysis among individual cancer types with sufficient sample size would allow further assessment of any heterogeneity in the effect of HIV on stage and treatment by cancer type.

Our study had several strengths, including the linkage between a cancer registry and HIV clinical cohort to directly compare cancer outcomes by HIV status among a collection of cancer registries that use the same data collection procedures. We were also able to perform sub-analyses by CD4 level to assess the role of immunosuppression in receipt of cancer treatment among PWH. Our use of random forest methods coupled with G-computation provided flexibility in determining the association of the covariates with outcomes of interest and an efficient estimator to offset the smaller sample size of those with HIV [18, 19, 21, 23]. Finally, individuals with cancer in the JHHCC are a largely non-Hispanic Black (78%), low income population with a high prevalence of hepatitis C co-infection (59%), and/or a history of injection drug use (39%), making it a unique population of PWH in which to explore cancer outcomes.

Conclusion

HIV infection was associated with a lower probability of being diagnosed with cancer at a local stage and a higher probability of being diagnosed with cancer a regional stage. Information on predictors of earlier detection of cancers among PWH would improve prognosis for these individuals. We did observed a lower probability of receiving initial cancer treatment by HIV status after accounting for demographic and cancer stage information. The role of HIV-related immune suppression in the receipt and tolerability of cancer treatment should be explored further.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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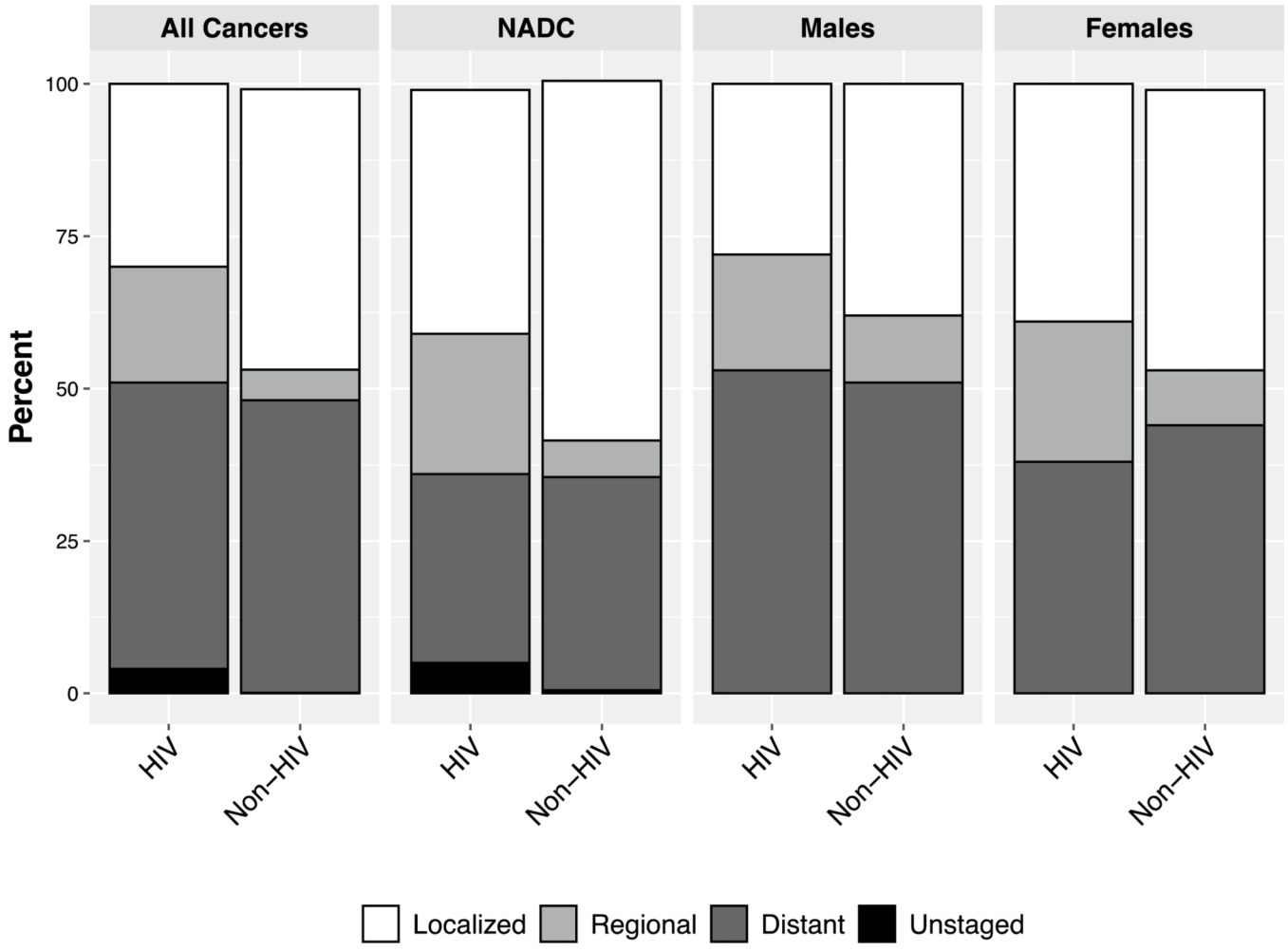

Fig. 1.

Distribution of stage at cancer diagnosis stratifed by HIV status for all cancers, non-AIDS-defning cancers (NADC), males, and females

[a] All models adjusted for age, sex, race, calendar year, and cancer type.

[b] Models among males and females do not include sex in the adjustment and excluded unstaged outcome due to small sample size.

Table 1

Percent receiving any cancer treatment among those with an incident, first cancer between 1997 and 2014 stratified by HIV status and the difference in percent receiving any cancer treatment (HIV–non-HIV)

Population	CD4 strata	HIV percent (95% CI)	Non-HIV percent (95% CI)	Difference (95% CI)
All cancers	All CD4	82 (76, 87)	94 (92, 97)	− 13 (− 18, − 8)
	CD4 ≤ 200	80 (67, 89)	94 (90, 99)	− 15 (− 27, − 6)
	CD4 > 200	85 (79, 91)	94 (91, 97)	− 9 (− 14, − 2)
NADC	All CD4	81 (75, 87)	93 (90, 96)	− 12 (− 18, − 5)
	CD4 ≤ 200	77 (61, 89)	91 (85, 98)	− 14 (− 29, − 4)
	CD4 > 200	83 (78, 91)	93 (90, 96)	− 10 (− 16, − 2)
Males	All CD4	79 (71, 85)	93 (90, 95)	− 14 (− 21, − 8)
	CD4 ≤ 200	81 (68, 92)	93 (86, 99)	− 12 (− 23, − 1)
	CD4 > 200	79 (71, 88)	92 (88, 96)	− 13 (− 20, − 3)
Females	All CD4	88 (80, 96)	95 (91, 98)	− 7 (− 15, 3)
	CD4 ≤ 200	75 (52, 93)	96 (89, 100)	− 20 (− 42, − 4)
	CD4 > 200	94 (89, 100)	94 (88, 100)	0 (− 8, 10)

NADC non-AIDS-defining cancer