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Article

CD4/CD8 Ratio and Cancer Risk Among Adults With HIV

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Abstract

Background: Independent of CD4 cell count, a low CD4/CD8 ratio in people with HIV (PWH) is associated with deleterious immune senescence, activation, and inflammation, which may contribute to carcinogenesis and excess cancer risk. We examined whether low CD4/CD8 ratios predicted cancer among PWH in the United States and Canada. **Methods:** We examined all cancer-free PWH with 1 or more CD4/CD8 values from North American AIDS Cohort Collaboration on Research and Design observational cohorts with validated cancer diagnoses between 1998 and 2016. We evaluated the association between time-lagged CD4/CD8 ratio and risk of specific cancers in multivariable, time-updated Cox proportional hazard models using restricted cubic spines. Models were adjusted for age, sex, race and ethnicity, hepatitis C virus, and time-updated CD4 cell count, HIV RNA, and history of AIDS-defining illness. **Results:** Among 83 893 PWH, there were 5628 incident cancers, including lung cancer (n = 755), Kaposi sarcoma (n = 501), non-Hodgkin lymphoma (n = 497), and anal cancer (n = 439). The median age at cohort entry was 43 years. The overall median 6-month lagged CD4/CD8 ratio was 0.52 (interquartile range = 0.30-0.82). Compared with a 6-month lagged CD4/CD8 of 0.80, a CD4/CD8 of 0.30 was associated with increased risk of any incident cancer (adjusted hazard ratio = 1.24 [95% confidence interval = 1.14 to 1.35]). The CD4/CD8 ratio was also inversely associated with non-Hodgkin lymphoma, Kaposi sarcoma, lung cancer, anal cancer, and colorectal cancer in adjusted analyses (all 2-sided $P < .05$). Results were similar using 12-, 18-, and 24-month lagged CD4/CD8 values. **Conclusions:** A low CD4/CD8 ratio up to 24 months before cancer diagnosis was independently associated with increased cancer risk in PWH and may serve as a clinical biomarker.

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Although people with HIV (PWH) are living longer with use of effective antiretroviral therapy (ART), they remain at an increased risk for cancer compared with the general US population (1–5). In addition to AIDS-defining cancers (ADCs), including Kaposi sarcoma, non-Hodgkin lymphomas (NHLs) and cervical cancer, risk of several non-ADC remains increased in PWH (6–9). Cancer mortality is also high among PWH (10,11). Approximately 10% of all deaths among PWH prescribed ART in the United States between 1995 and 2009 were attributed to cancer, with NHL, lung, and liver cancer contributing the highest number of deaths (10).

Cancer risk in PWH is attributed to immunodeficiency, immune dysfunction, and high prevalence of oncogenic virus coinfection (including human papillomavirus [HPV] and hepatitis C virus [HCV]) and behavioral risk factors, including smoking (12–15). In addition to immunodeficiency, decreased immune surveillance and increased cellular replication associated with immune senescence, activation, and inflammation increase carcinogenesis (16,17). In PWH, CD4 and CD8 cell counts are clinically readily available. A low CD4/CD8 ratio inversely correlates with T lymphocyte replicative senescence, activation, and exhaustion, each a measure of immune senescence and systemic inflammation (18–20). A low CD4/CD8 ratio is also associated with older age, cytomegalovirus coinfection, and low CD4 cell count nadir, and has been associated with risk of non-AIDS outcomes (18,21–27). We sought to determine whether the CD4/CD8 ratio, as a marker of immune dysfunction, was associated with cancer risk, with the hypothesis that the CD4/CD8 ratio would be inversely associated with incident cancer diagnoses among PWH.

Methods

Study Population

We examined incident cancer diagnoses and longitudinal CD4/CD8 data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) (28). Participating cohorts contributed patient-level demographic, behavioral, and clinical data, including diagnoses, medications, and laboratory values, to the central Data Management Center for quality assessment and harmonization. All cancer diagnoses were validated by standardized medical record documentation that included abstraction of histopathologic information or linkage with cancer registries (4). The institutional review boards at participating cohorts, Johns Hopkins University, and Vanderbilt University have approved human patient activities conducted within the NA-ACCORD related to this study.

NA-ACCORD includes PWH aged 18 years or older with at least 2 clinic visits within the first year of cohort enrollment. A total of 22 observational cohorts in NA-ACCORD collected validated cancer diagnoses from January 1998 to December 2016. Seven cohorts were excluded where 25% or more of PWH had no CD8 cell counts data. All PWH with any cancer diagnosis before or within the first 6 months of cohort entry or a cancer with an unknown diagnosis date were excluded. Only PWH with a minimum of 12 months of clinic follow-up were included in the primary analysis to allow for our lagged exposure (see below). PWH contributed person-time of observation from 6 months after cohort entry until cancer diagnosis, death, last laboratory value if longer than 18 months before cohort data closure, or date of validated cancer data closure. PWH with extended periods out of care (defined as >18 months without laboratory values) were allowed to reenter the observation period.

Our primary outcomes were incident invasive cancers, excluding basal and squamous cell skin cancers (due to inadequate capture or data in some cancer registries). We examined any incident cancer diagnosis as a composite outcome as well as individual ADCs (Kaposi sarcoma, NHL, and cervical cancer), other viral-associated cancers (Hodgkin lymphoma, liver, anal, head and neck cancers), and nonviral associated cancers (lung, breast, colorectal cancer, and prostate cancers). For those PWH with multiple cancers, only the first such diagnosis was included as an outcome.

We used time-updated, lagged values of CD4/CD8 ratio in our time-to-event analyses. We hypothesized a delayed effect of CD4/CD8 ratio and cancer diagnosis; therefore, we evaluated lagged CD4/CD8 ratio values, referencing the values recorded during defined intervals in the past in estimation of cancer risk during observation time (Supplementary Figure 1, available online). Individual observation time was constructed based on laboratory values and their corresponding dates of measurement. CD4 and CD8 cell counts were time-varying and carried forward for a maximum of 1 year. In the setting of a gap in laboratory values of more than 1 year, the remaining person-time was coded as missing laboratory values, and the gap period was excluded from the analysis. Person-time of observation, including cancer diagnoses occurring during periods of missing laboratory values, were censored. Our primary analysis examined the 6-month lagged CD4/CD8 ratio value to minimize risk of reverse causality of CD4/CD8 ratio changes and cancer diagnosis. Given that the time between a low CD4/CD8 ratio and cancer development is not known, we repeated analyses using 12-month, 18-month, and 24-month lagged CD4/CD8 ratios.

Statistical Analysis

Multivariable Cox proportional hazards models estimated cause-specific hazard ratios for CD4/CD8 ratio and cancer risk (29). Assumption of proportionality of the primary exposure variable was tested by a global test based on Schoenfeld residuals and visual residual plots checking. Individuals were followed to their first cancer outcome or were censored if they died or had no event during their observed follow-up time. Multivariable models included covariates selected a priori based on clinical knowledge and number of events (degrees of freedom) as potential confounders of the association between CD4/CD8 ratio and each cancer outcome, other cancers, or death. All models included age at study entry, race and ethnicity (Black, Latinx, other [which included Asian, Indigenous, Multiracial, Other, and unknown race], or White), sex, cohort entry year, any history of HCV infection, and time-varying history of any AIDS-defining illness (excluding ADC). Statistical interaction terms were added to examine whether associations between race and ethnicity and CD4/CD8 ratio altered risk for any cancer. Models examining risk factors for liver cancer additionally adjusted for prior hepatitis B virus infection, injection drug use, heavy alcohol use (defined by documented diagnoses, medical record review, and survey results), and time-varying, lagged diagnosis of cirrhosis. Models including time-varying lagged CD4 cell count and HIV RNA examined the effect of CD4/CD8 ratio (independent of absolute CD4 cell count) and accounted for the strong correlation between HIV viremia and the absolute CD4 and CD8 cell count. HIV RNA (log_{10} transformed), CD4 count (square root transformed), and CD4/CD8 ratio (natural logarithm transformed) were modeled as time-varying covariates. HIV RNA was used as a surrogate marker for time-varying ART use, and

values below the limit of detection were calculated as (lower limit of detection − 1 copy/mL). To avoid assuming a linear relationship, most continuous covariates were included using restricted cubic splines, including CD4/CD8 ratio (30). Consistent referent values were important for comparison of effects for each cancer analysis. We present adjusted hazard ratios for the CD4/CD8 ratio comparing the 0.3 and 0.5 with 0.8 values for comparison and approximation to the 25th, 50th, and 75th percentile values of the 6-month lagged CD4/CD8 ratio values for the study cohort. *P* values were computed using Wald statistics. Breast and cervical cancer analyses included only females; prostate cancer analyses included only males. Covariates were selected a priori based on biologic plausibility and not by stepwise selection. The number of covariates for each model was based on the number of outcomes and available degrees of freedom (approximately 10 events per covariate). Due to the small number of events, covariates for models for breast and cervical cancers included those hypothesized to be the most important potential confounders (CD4 cell count, HIV RNA, age, race and ethnicity, and prior AIDS-defining event). We stratified all Cox analyses by cohort to allow for separate baseline hazards.

In sensitivity analyses, primary multivariable models were repeated, replacing the CD4/CD8 ratio with time-lagged, square-root transformed absolute CD8 cell count and using restricted cubic splines to explore individual effects of the CD4/CD8 ratio. Given the effects of ART on the CD4/CD8 ratio, we additionally repeated 6- and 12-month lagged CD4/CD8 ratio multivariable analyses for all cancers censoring person-time corresponding to laboratory results obtained before ART initiation. Another analysis fitted models that included HIV acquisition risk factor; smoking status (ever vs never); and 6-month lagged, time-varying body mass index. When smoking status or alcohol was missing for individual patients, we used covariates and the outcome data to multiply impute (20 times) using predictive mean matching. Estimates from the imputation-specific analyses were then combined using Rubin's rule (31).

All analyses were conducted in R version 3.6.2, and the analysis code is available online at https://biostat.app.vumc.org/wiki/Main/ArchivedAnalyses. All *P* values were 2-sided, and the cut point for statistical significance was .05.

Results

The study population from the 15 eligible cohorts with contributing data is shown in Supplementary Figure 2 (available online). Characteristics of PWH included in the primary and sensitivity analyses are shown in Table 1. In the primary analysis using 6-month lagged laboratory data, 83 893 PWH contributed 744 415 person-years of observation and 5628 incident cancer diagnoses. Of all observation time, 167 816 person-years (22.5%) were censored for the missing CD4/CD8 ratio or HIV RNA levels. The median 6-month lagged CD4/CD8 ratio was 0.52 (interquartile range = 0.30-0.82). PWH in both the primary and sensitivity analyses were predominantly male, and less than one-half were White. The median CD4 cell count, HIV RNA, and history of AIDS-defining illness at the start of observation time was similar between PWH included in the primary and sensitivity analyses. Table 1 shows the frequency of the most common cancers diagnosed. For the primary analyses, there was a total of 5628 incident cancers, of which Kaposi sarcoma (n = 501), NHL (n = 497), prostate cancer (n = 817), lung cancer (n = 755), and anal cancer (n = 439) were the most frequent.

Figure 1 shows the adjusted hazard ratios and 95% confidence intervals (CIs) comparing the 0.3 and 0.5 with the 0.8 CD4/CD8 ratio values of our primary analysis. There was a 24% increased risk of any incident cancer for individuals with a 6-month lagged CD4/CD8 ratio of 0.3 compared with 0.8, independent of CD4 cell count, HIV RNA value, and other covariates (adjusted hazard ratio [aHR] = 1.24, 95% CI = 1.14 to 1.35). We observed the same pattern of increasing cancer risk with decreasing CD4/CD8 ratio for NHL, Kaposi sarcoma, lung cancer, anal cancer, and colorectal cancer. The 6-month-lagged CD4/CD8 ratio was not associated with risk of cervical cancer, Hodgkin lymphoma, head and neck cancer, prostate cancer, breast cancer, or liver cancer. We similarly observed an inverse association of CD4/CD8 ratio and risk of any cancer for all race and ethnicity groups, though the magnitude of the CD4/CD8 ratio effect on outcome varied by race (interaction term overall *P* value <.001) (Supplementary Figure 3, available online).

Supplementary Table 1 (available online) shows results examining the 6-month, 12-month, 18-month, and 24-month lagged CD4/CD8 ratio values. Adjusted hazard ratios for cancers common among PWH along a continuum of CD4/CD8 values compared with 0.8 and using different lags are shown in Figure 2. Overall, we observed differing patterns of timing of low CD4/CD8 ratio and cancer risk across cancer types. Low CD4/CD8 ratio values from 6 to 24 months prior were all associated with increased risk of any cancer ($P < .001$ for all time points). Similarly, a low CD4/CD8 ratio was strongly associated with increased risk of anal and lung cancers across all lagged time points ($P < .001$ for all time points for both cancers) (Figure 2). In contrast, although statistically significant at all lagged time points, a low CD4/CD8 ratio was associated with highest risk of NHL in the 6 months prior compared with 24 months (Figure 2D, $P < .01$ for all lagged time points). In contrast, a low CD4/CD8 ratio 6 months prior was not associated with risk of Hodgkin lymphoma ($P = .88$) but was associated with increased risk 12 and 18 months prior ($P = .05$ and .02, respectively) (Figure 2). Additional figures for specific cancer types and lagged CD4/CD8 ratio values are shown in Supplementary Figure 4 (available online). Results of models restricted to include only person-time after ART initiation were very similar to results including all person-time (Supplementary Table 2, available online). Results of 6-month lagged models that included absolute CD8 cell count rather than CD4/CD8 ratio were consistent with our primary analyses: high CD8 and low CD4 were generally associated with increased hazards of cancers (Supplementary Figure 5, available online).

The multivariable analyses including the subset of patients with available smoking, alcohol, HIV acquisition risk factor, and body mass index data that assessed 6-month lagged CD4/CD8 ratio and cancer risk are shown in Figure 3. Given the smaller number of cancers included in the sensitivity analyses, only any cancer, NHL, Kaposi sarcoma, lung cancer, and anal cancer were assessed in multivariable models to avoid overfitting. The inverse association between low CD4/CD8 ratio and increased cancer risk persisted for any cancer, NHL, lung cancer, and anal cancer but was attenuated and no longer statistically significant for Kaposi sarcoma.

Discussion

In this large study of PWH in care and with high uptake of ART between 1998 and 2016, we found that a low, time-lagged CD4/CD8 ratio was associated with increased risk of incident cancer

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Table 1. Baseline patient characteristics and outcomes of people living with HIV included in primary and sensitivity analyses of 6-month lagged laboratory data

Baseline characteristics and outcomes	Primary analysis (N = 83 893)	Sensitivity analysis (N = 40 975)
Sex, No. (%)		
Male	72 709 (86.7)	32 420 (79.1)
Female	11 184 (13.3)	8555 (20.9)
Median age at study entry (IQR), y	42.5 (35.1-50.4)	39.5 (32.5-46.8)
Race and ethnicity, No. (%)		
Black	31 252 (37.3)	12 283 (30.0)
Latinx	9449 (11.3)	5728 (14.0)
Other or unknown[a]	6898 (8.2)	3316 (8.1)
White	36 294 (43.3)	19 648 (48.0)
HIV transmission risk factor, No. (%)		
Men who have sex with men	28 725 (34.2)	24 368 (59.5)
Injection drug use	16 264 (19.4)	4200 (10.3)
Heterosexual	10 927 (13.0)	9222 (22.5)
Other	2015 (2.4)	1007 (2.5)
Unknown or missing	25 962 (30.9)	2178 (5.3)
Chronic hepatitis C virus infection, No. (%)	17 855 (21.3)	6816 (16.6)
Chronic hepatitis B virus infection, No. (%)	5991 (7.1)	3023 (7.4)
Any history of heavy alcohol use[b], No. (%)	24 623 (29.4)	11 500 (28.1)
Any history of tobacco use[c], No. (%)	28 373 (33.8)	24 201 (59.1)
Median CD4 cell count (IQR), cells/μL[d]	413 (243-610)	433 (262-631)
Median CD4/CD8 ratio[e] (IQR)	0.47 (0.27-0.76)	0.50 (0.29-0.78)
Median Log_{10} HIV RNA (IQR), copies/mL[f]	2.3 (1.7-3.9)	2.1 (1.7-3.8)
HIV RNA[f], No. (%)		
<500 copies/mL	41 470 (58.3)	23 670 (59.7)
500-4999 copies/mL	9807 (13.6)	5187 (13.1)
≥5000 copies/mL	19 844 (27.9)	10 784 (27.2)
Median body mass index (IQR), kg/m^2 [g]	25.2 (22.7-28.5)	25.2 (22.6-28.5)
History of AIDS-defining illness, No. (%)	11 438 (13.6)	7035 (17.2)
Geographic region of clinical care[h], No. (%)		
US Northeast	10 788 (12.9)	3632 (8.9)
US Midwest	7403 (8.8)	2993 (7.3)
US Southeast	20 483 (24.4)	7283 (17.8)
US West	28 363 (33.8)	19 209 (46.9)
US Southwest	4444 (5.3)	111 (0.3)
US Puerto Rico and Virgin Islands	585 (0.7)	2 (0.0)
Canada	6733 (8.0)	3293 (8.0)
Other	12 (0.0)	2 (0.0)
Unknown	5082 (6.1)	4450 (10.9)
Median duration of follow-up (IQR), y	8.5 (4.0-13.8)	7.7 (3.6-12.7)
Initiated antiretroviral therapy before study exit[i], No. (%)	75 201 (89.6)	37 029 (90.4)
Proportion of follow-up time after antiretroviral therapy initiation, No. (%)		
<10%	834 (1.0)	388 (0.9)
10%-24%	895 (1.1)	382 (0.9)
25%-49%	2171 (2.6)	857 (2.1)
50%-74%	4108 (4.9)	1868 (4.6)
75%-89%	4042 (4.8)	1935 (4.7)
≥90%	63 528 (75.7)	31 806 (77.6)
Missing antiretroviral therapy data	8315 (9.9)	3739 (9.1)
Died, No. (%)	14 345 (17.1)	4062 (9.9)
Any incident cancer[j], No. (%)	5628 (6.7)	2172 (5.3)
AIDS-defining cancers, No. (%)		
Non-Hodgkin lymphoma	497	251
Kaposi sarcoma	501	253
Cervix	47	41
HIV-associated cancers, No.		
Lung	755	186
Anus	439	209
Liver	347	74
Hodgkin lymphoma	176	84
Head and neck	134	60
Other, No.		
Prostate	817	163
Colorectum	221	69
Breast	79	61
Other	1615	721

[a]Other race and ethnicity included Asian, Indigenous, Multiracial, Other, and unknown race. IQR = interquartile range.
[b]Ever documentation of alcohol abuse or at-risk alcohol use. Total of 2165 (3%) missing in primary analysis, 80 (0%) missing in sensitivity analysis.
[c]Ever documentation of tobacco usage. Total of 43 253 (52%) missing in primary analysis, 5660 (14%) missing in sensitivity analysis.
[d]CD4 cell count at baseline (closest values within 6 months before or after). Total of 13 170 (16%) missing in primary analysis, 1197 (3%) missing in sensitivity analysis.
[e]CD8 and CD4/CD8 ratio at baseline (closest values within 6 months before or after). Total of 15 915 (19%) missing in primary analysis, 2198 (5%) missing in sensitivity analysis.
[f]HIV RNA at baseline (closest values with 6 months before or 30 days after). Total of 12 772 (15%) missing in primary analysis, 1334 (3%) missing in sensitivity analysis.
[g]Body mass index at baseline (closest values within 6 months before or after). Total of 21 989 (26%) missing in primary analysis, 3994 (10%) missing in sensitivity analysis.
[h]Geographic regions refers to location recorded closest to date of cohort entry. Other locations include Armed Forces Africa, Europe, Middle East, and Pacific and Guam.
[i]Study exit includes earliest occurrence of first cancer, death, or administrative censoring. ART data missing for 8315 (9.9%) in primary analysis and 3739 (9%) in sensitivity analysis.
[j]Any incident cancer excludes nonmelanoma skin cancers.

diagnoses after accounting for CD4 cell count, HIV viral load, HIV acquisition risk, smoking, and other factors. The inverse association between CD4/CD8 ratio and cancer risk was observed for several specific cancers, including 3 of the most common cancers among PWH in the United States: NHL, lung cancer, and anal cancer. The association between low CD4/CD8 ratio and risk of cancer was not uniform, nor was the association exclusive for cancers associated with oncogenic viruses. Given the robust association up to 24 months before cancer diagnosis, the CD4/CD8 ratio may indicate underlying immune dysfunction affecting carcinogenesis and inform cancer screening and prevention interventions among PWH.

A low CD4/CD8 ratio predicted risk of any cancer, independent of age, sex, CD4 cell count, HIV viral load, chronic HCV infection, and smoking history measures. Among PWH, a low CD4/CD8 ratio is associated with older age, low CD4 nadir, male sex, HIV acquisition risk factors (particularly for men who whave sex with men), chronic viral coinfection (including HCV and cytomegalovirus), and large HIV reservoir (27,32–35).

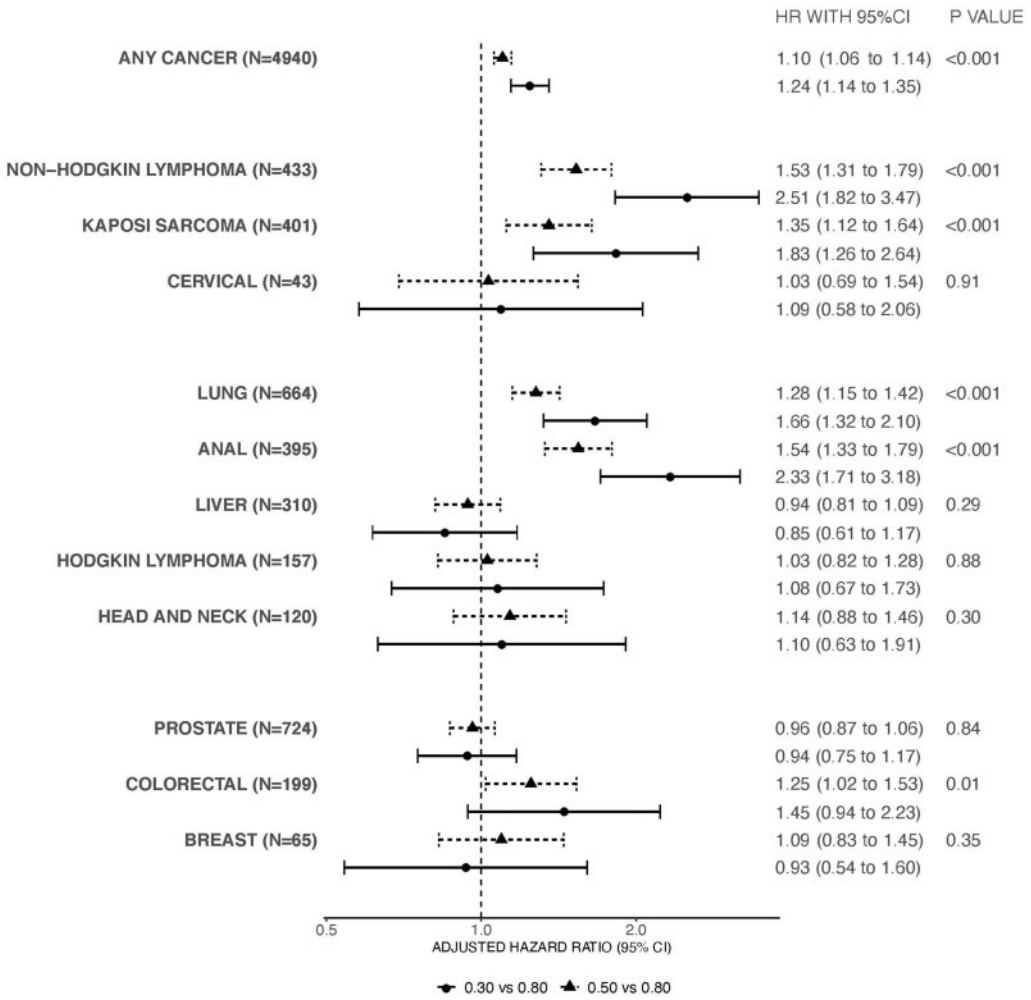

Figure 1. Adjusted hazard ratios (HR) and 95% confidence interval (CI) for cancer risk comparing the 6-month lagged, time-varying CD4/CD8 ratio values. Models for any cancer, lung cancer, non-Hodgkin lymphoma, Hodgkin lymphoma, Kaposi sarcoma cancer, anal cancer, head and neck cancer, colorectal cancer included the covariates of age, sex, race and ethnicity, year of cohort entry, any history of chronic hepatitis C virus infection, and time-varying and time-updated CD4/CD8 ratio, CD4 cell count, HIV RNA, and history of AIDS-defining illness. The multivariable model for liver cancer included the covariates of age, sex, race, year of cohort entry, any history of chronic hepatitis C virus infection, history of chronic hepatitis B virus infection, history of heavy alcohol use, history of injection drug use, and time-varying and time-updated CD4/CD8 ratio, CD4 cell count, HIV RNA, history of AIDS-defining illness, and history of cirrhosis. The multivariable model for prostate cancer included only males and covariates age, race, year of cohort entry, any history of chronic hepatitis C virus infection, and time-varying and time-updated CD4/CD8 ratio, CD4 cell count, HIV RNA, and history of AIDS-defining illness. Models for breast cancer and cervical cancer included only females and included age, race (White vs non-White), and time-varying and lagged CD4/CD8 ratio, CD4 cell count, HIV RNA, and history of AIDS-defining illness. The **error bars** represent the 95% confidence intervals. Wald statistic was used to calculate *P* values (2-sided). **Circles** represent the adjusted hazard ratio comparing a CD4/CD8 value of 0.30 vs a CD4/CD8 value of 0.80. **Triangles** represent the adjusted hazard ratio comparing a CD4/CD8 value of 0.50 vs a CD4/CD8 value of 0.80.

Despite immune reconstitution from effective ART, PWH with a low CD4/CD8 ratio have increased measures of adaptive immunosenescence, including skewed T-lymphocyte populations from naïve to terminally differentiated phenotypes, higher expression of cellular markers of CD8 T-cell activation and senescence, and a higher kynurenine to tryptophan ratio (18,20). A low CD4/CD8 ratio has also been associated with increased measures of monocyte activation and systemic inflammatory measures, including interleukin 6 (IL-6), C-reactive protein (CRP), and soluble CD14 (18,19). Adaptive immune senescence, T-cell activation, and inflammation have been identified as drivers of the excess risk of noncommunicable diseases observed in PWH, including cardiovascular disease and cancers (36–39). In PWH, a low CD4/CD8 ratio has been associated with increased risk of mortality and noncommunicable diseases (22,23,40). A low CD4/CD8 ratio has been associated with risk of non-ADCs in smaller studies of PWH (24,41). To our knowledge, this is the largest study to demonstrate an independent association between a low CD4/CD8 ratio and cancer risk in PWH, which we found was consistent up to 2 years preceding the cancer diagnosis.

NHL, lung cancer, and anal cancer, 3 of the leading causes of cancer-related morbidity and mortality in PWH in the United States, were strongly and consistently associated with a low CD4/CD8 ratio (42). Both lung cancer and anal cancer have higher incidence and are diagnosed at younger ages in PWH compared with the general population, suggesting accelerated aging biology, such as immunosenescence, may contribute to cancer risk in PWH (6,8,43,44). The large Veterans Aging Cohort Study found an independent association between a low, cumulatively averaged CD4/CD8 ratio and lung cancer risk in US veterans with HIV (25). Our results are consistent with their

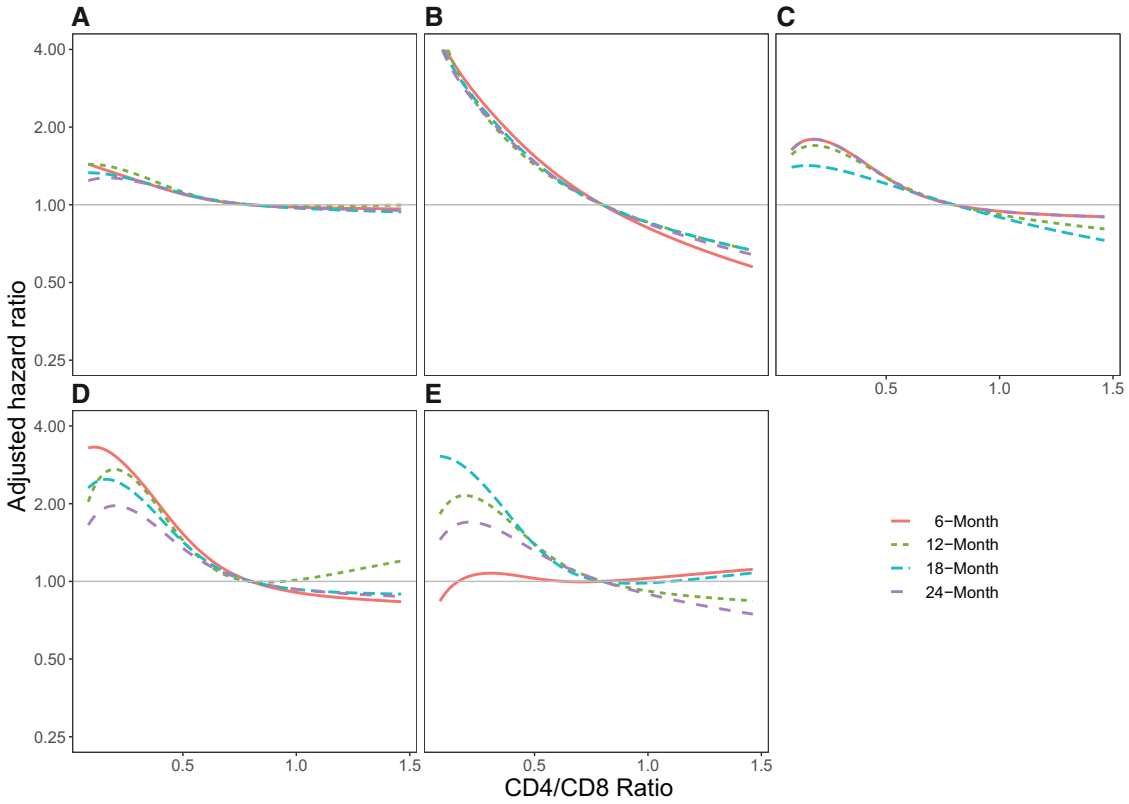

Figure 2. Adjusted hazard ratio for cancer risk and CD4/CD8 ratios lagged 6, 12, 18, and 24 months. Adjusted hazard ratio for CD4/CD8 ratio values lagged 6 months (**solid orange lines**), 12 months (**dashed green lines**), 18 months (**dashed teal lines**), and 24 months (**dashed purple lines**) for the following cancers (number of events for each model): **A)** any cancer (6 months n = 4940; 12 months n = 4597; 18 months n = 4308; 24 months n = 4043); **B)** anal cancer (6 months n= 395; 12 months n = 375; 18 months n = 361; 24 months n = 340); **C)** lung cancer (6 months n = 664; 12 months n = 645; 18 months n = 645; 24 months n = 564); **D)** non-Hodgkin lymphoma (6 months n = 433; 12 months n = 382; 18 months n = 333; 24 months n = 310); **E)** Hodgkin lymphoma (6 months n = 157; 12 months n = 145; 18 months n = 143; 24 months n = 124). Models included the covariates of age, year of cohort entry, sex, race and ethnicity, any history of chronic hepatitis C virus infection, and time-varying and lagged CD4/CD8 ratio, CD4 cell count, HIV RNA, and history of AIDS-defining illness.

findings, supporting the hypothesis that immune dysfunction may contribute to cancer risk in PWH.

This is the largest study to show that a low peripheral CD4/CD8 ratio predicts anal cancer risk, independent of HIV acquisition risk factor, smoking, or immunodeficiency. A single-center study of PWH observed that a low CD4/CD8 ratio nadir and CD4/CD8 proximal to anal cancer screening were associated with high-grade anal dysplasia and cancer; however, the analyses did not adjust for concurrent CD4 cell count (45). The ratio of CD4/CD8 tumor-infiltrating and stromal lymphocytes in tissue biopsies of HPV-associated precancers of the cervix, anus, and head and neck have been associated with disease progression or regression; however, the circulating CD4/CD8 ratio has not been evaluated in anal precancers (46–49). ART has not been shown to be associated with the regression or clearance of anal lesions, suggesting immune restoration does not entirely eliminate the increased risk (50,51). That we did not find an association between CD4/CD8 ratio and cervical cancer may be due to the small number of cancer cases in this cohort. Although we did not find a statistically significant association between CD4/CD8 ratio and head and neck cancer, we could not distinguish cases that were associated with HPV. Further research is needed to assess CD4/CD8 ratio and HPV-associated and HPV-negative head and neck cancers.

It is worth noting that because our analyses adjusted for CD4 count, the observed inverse association between the CD4/CD8 ratio and risk of cancer reflects an association between higher CD8 cell count and higher risks of cancer. Our sensitivity analyses that replaced the CD4/CD8 ratio with absolute CD8 cell count demonstrated this relationship. We chose to present results using the CD4/CD8 ratio rather than CD8 cell count for consistency with the literature and the convenience of including CD4 and CD8 cell counts in a single measure; however, CD4 and CD8 could alternatively be considered in tandem as biomarkers for cancer.

There are important limitations of this study. Additional modeling and prospective studies are needed to translate how and when CD4/CD8 ratio can best be used in cancer screening in clinical care for PWH. These studies will need to account for differences in the association of the CD4/CD8 ratio for specific cancers as well as investigate differences by demographic and time-varying clinical (such as time since ART initiation, CD4 cell count nadir, and current CD4 cell count) characteristics among PWH. Our investigation revealed an interaction between race and ethnicity and the association CD4/CD8 ratio and any cancer outcome. Additional investigation into whether and how individual characteristics among PWH (including race, sex, age, and clinical history) affect the association of the CD4/CD8 ratio and specific cancer outcomes are needed. Our study population was disproportionately male, not only resulting in low numbers of cervical cancer and breast cancer but also limiting our ability to examine CD4/CD8 ratio and cancer risk in women with HIV more generally. HIV acquisition risk factor and behavioral data including smoking history were not available from all cohorts,

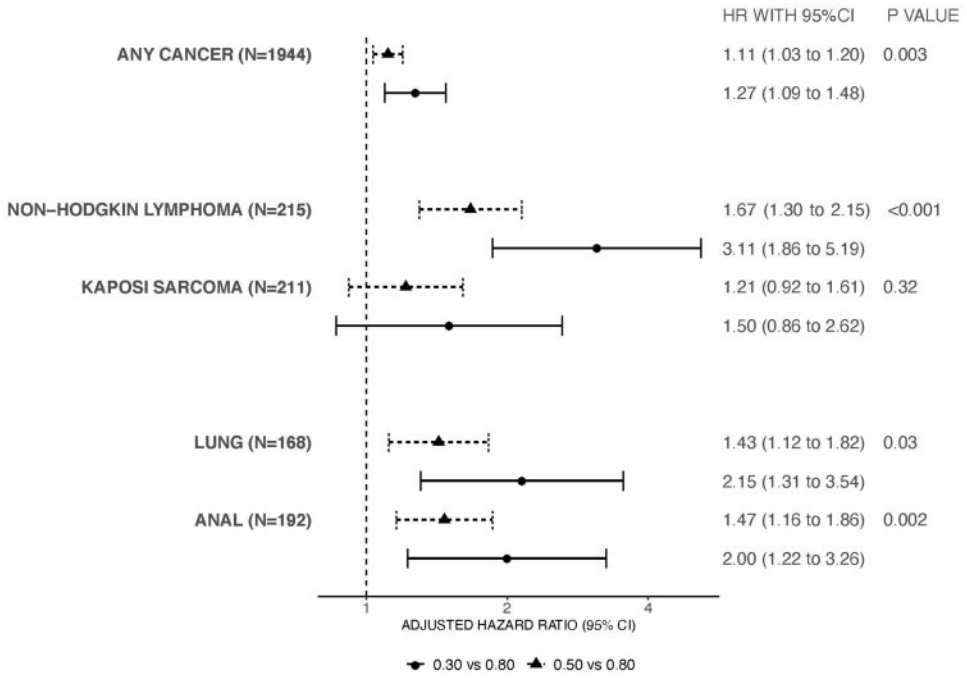

Figure 3. Sensitivity analyses including additional behavioral and body mass index covariates for the adjusted hazard ratios and 95% confidence interval (CI) for cancer outcomes comparing the 6-month lagged, time-varying CD4/CD8 ratio values. Only models for any cancer, lung cancer, non-Hodgkin lymphoma, Kaposi sarcoma cancer, and anal cancer performed due to number of events. All models included the covariates of age, sex, race, year of cohort entry, any history of chronic hepatitis C virus infection, history of smoking, history of heavy alcohol use, HIV acquisition risk factor, and time-varying and time-updated CD4/CD8 ratio, CD4 cell count, HIV RNA, history of AIDS-defining illness, and body mass index. The **error bars** represent the 95% confidence intervals. Wald statistic was used to calculate *P* values (2-sided). **Circles** represent the adjusted hazard ratio comparing a CD4/CD8 value of 0.30 vs a CD4/CD8 value of 0.80. **Triangles** represent the adjusted hazard ratio comparing a CD4/CD8 value of 0.50 vs a CD4/CD8 value of 0.80.

though results from our sensitivity analyses were generally consistent with those from the primary analyses. However, for lung cancer in particular, our results may still be affected by residual confounding from smoking given the limited smoking information in our cohort. The CD4/CD8 ratio is lower in settings of chronic viral infections, and our data on prevalent oncogenic viruses were limited to HCV and hepatitis B virus. The cancer most associated with these viruses, liver cancer, was not statistically significantly associated with the CD4/CD8 ratio in multivariable models. Seroprevalence of cytomegalovirus, human herpes virus 8 (Kaposi sarcoma), Epstein-Barr virus (Hodgkin lymphoma and NHL), or infection with high-risk HPV (cervical, anal, and head and neck cancers) is not universally collected in clinical care of PWH. We used lagged CD4/CD8 ratio values to reduce the risk that cancer itself is causing a low CD4/CD8 ratio; however, it is possible that 6 months may not be sufficient to eliminate this possibility. Reassuringly, results examining 12-month and up to 24-month lagged values were consistent with the 6-month lagged results. Our data may also be subject to misclassification bias as a result of carrying forward CD4/CD8 data and periods of missing CD4/CD8 data.

In the largest study of PWH in the United States and Canada, we found that a lagged, low CD4/CD8 ratio was associated with increased risk of certain incident cancers. A low CD4/CD8 ratio was associated with increased risk of NHL, lung cancer, and anal cancer. The consistency of association observed up to 24 months before cancer diagnosis suggests the CD4/CD8 ratio may be a useful biomarker for screening for lung and anal cancer in PWH where the average age at diagnosis is younger than in the general population. Further investigation into the roles of immunosenescence, immune activation, and inflammation and cancer risk observed in PWH is needed.

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Data Availability

NA-ACCORD welcomes interested investigators to collaborate with us for use of our data. Please visit https://naaccord.org/ for additional information.

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