

Cancer incidence and risk factors among people with HIV in REPRIEVE

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Objective: Cancer is a leading cause of morbidity and mortality among people with HIV (PWH), who face a greater risk than the general population. An enhanced understanding of cancer incidence and associated risk factors among PWH receiving effective antiretroviral therapy (ART) may guide targeted preventive interventions.

Design and methods: Analyses included REPRIEVE participants without cancer at baseline, followed until first cancer incidence or trial end. Incidence rates were computed for all cancers, AIDS-defining cancers (ADCs), non-AIDS-defining cancers (NADCs), both infection-related and noninfection-related, by Global Burden of Disease (GBD) region and sex. Cause-specific Cox models assessed associations with traditional [age, sex, region, body mass index (BMI), smoking] and HIV-related (nadir CD4, baseline CD4, CD4/CD8 ratio) factors.

Results: Among 7507 participants (31.5% women) with median follow-up of 5.6 (Q1–Q3: 4.6–6.3) years, 219 incident cancers occurred [incidence rate (IR): 5.6 per 1000 person-years, 95% confidence interval (CI): 4.9–6.4]. Noninfection-related NADCs were most common (3.4 [2.8–4.0]), followed by infection-related NADCs (1.5 [1.1–1.9]) and ADCs (0.6 [0.4–0.9]). Incidence was higher in males and participants from high-income countries. Leading cancers included prostate, breast, lung, and anal. Older age, high-income country residence, and current smoking were independently associated with higher cancer risk, whereas sex, BMI, and HIV-related factors were not.

Conclusions: In a global cohort of PWH on effective ART, cancer remains an important comorbidity, with risk varying by demographic and behavioral factors. Targeted prevention strategies, particularly smoking cessation and age- and region-specific cancer screening approaches, may help reduce cancer burden in this population.

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Introduction

People with HIV (PWH) are facing an increased risk of developing cancer compared to people without HIV (PWoH) [1–4]. While mortality rates for PWH declined dramatically with the advent of potent antiretroviral therapy (ART) [5], cancer remains an important cause of morbidity and the leading cause of mortality among PWH [6–8]. Additionally, the distribution of cancer types among PWH has changed, largely due to treatment advances and longer survival of this population, shifting from acquired immune deficiency syndrome (AIDS)-defining cancers (ADCs) towards non-AIDS-defining cancers (NADCs) [9–12]. Cancer incidences vary markedly across geographic regions and are significantly affected by population characteristics, availability of ART, and access to healthcare [13–18].

Among PWH, the risk of certain cancer types has been closely linked to HIV induced immunosuppression, chronic inflammation, and coinfection with oncogenic pathogens, including Epstein–Barr virus (EBV), human herpesvirus 8 (HHV-8), human papillomavirus (HPV), and hepatitis B and C viruses (HBV, HCV) [19–21]. Additionally, the higher prevalence of other major cancer risk factors in PWH, such as cigarette smoking, is thought to contribute to the increased risk of specific cancers including lung and anal cancer [22–25]. As PWH globally experience longer lifespans, age-related cancers (e.g., prostate, breast, and colorectal cancers) are becoming more common in this population [5,19,20,26,27]. Other potential cancer risk factors, including oncogenic effects of the HIV virus itself and certain ART medications, have also been studied, but their associations with cancer remain inconclusive [28–31]. This study extends our prior work in the REPRIEVE trial, which demonstrated that pitavastatin did not significantly reduce non-AIDS-defining cancers or AIDS-defining events in a diverse, global cohort of ART-treated HIV population [32]. In the present analysis, we quantify the incidence of cancers and their subtypes in the entire REPRIEVE cohort, stratified by sex, and by Global Burden of Disease (GBD) regions. By leveraging baseline data on traditional and HIV-specific risk factors, we also aimed to identify risk factors associated with cancer among a global population of PWH who were well treated on ART and had access to medical care. A better understanding of the relative contributions of risk factors to cancer development will help identify PWH at an increased risk of cancer and inform improved prevention strategies.

Methods

Study population

This study analyzed participants from the REPRIEVE trial without a history of cancer at study entry. Individuals diagnosed with metaplasia were deemed eligible and included in the final analysis [33]. REPRIEVE is a phase 3 randomized trial of 7769 PWH (aged 40–75) enrolled 2015–2019 and followed for a median of 5.6 years. The methodology and characteristics of the REPRIEVE cohort are described in detail elsewhere [34]. Of note, participants were required to be on a stable ART regimen of any combination for ≥ 6 months prior to study entry, have a $CD4^+$ T-cell count >100 cells/ μ l, and low-to-moderate traditional atherosclerotic cardiovascular disease (ASCVD) risk. Over 100 clinical sites from 12 countries participated in REPRIEVE and their GBD regions are high income regions (HICs: Canada, Spain, and USA) and low- and middle-income regions (LMICs: Latin America and the Caribbean, southeast and east Asia, south Asia, and sub-Saharan Africa). The study was approved by the Mass General Brigham Institutional Review Board.

Risk factors and outcome measures

Risk factors for incident cancer event were defined *a priori* and categorized as traditional (including geospatial) or HIV-related, based on variables assessed at study entry and previously identified associations [35–38]. Traditional risk factors included sex, age (continuous and categorized as 40–49, 50–59, and ≥ 60 years) [39,40], GBD region, body mass index (BMI, race-specific cutoffs for low, normal, overweight, and obese) [39,40], and smoking status (current, former, and never smoked). HIV-related risk factors were baseline $CD4$ count (using the clinical cutoffs of 200, 350, and 500 cells/ mm^3), nadir $CD4^+$ cell count (categorized by cutoffs of 50, 200, and 350 cells/ mm^3), and $CD4/CD8$ ratio (categorized by cutoffs of 0.5 and 1). Although HIV viral load has been identified as an important risk factor for cancers in several previous studies, we chose not to include it in the present analysis given that all REPRIEVE participants were ART-treated and only 2% exhibited a detectable viral load (>400 copies/ml) at study entry, resulting in insufficient variability for stable regression estimation.

Cancer was a prespecified secondary endpoint of the REPRIEVE trial. In accordance with the protocol, new cancer diagnoses made since the preceding study visit were captured by sites from medical records as targeted clinical events and collected through a targeted questionnaire at each visit. If a new cancer event was reported, information captured included diagnosis date and level of

certainty. Two authors (CJF, CDM) independently verified diagnoses, resolving discrepancies through site queries; only “confirmed” or “probable” cancer events were included in the analysis [32].

The primary outcome was any incident cancer event. Cancers were further classified as ADCs, infection-related NADCs, or noninfection-related NADCs (Table S1, Supplemental Digital Content, <https://links.lww.com/QAD/D973>) per trial protocol and previously published classifications [3,32]. ADCs included Kaposi's sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer. NADCs were categorized as infection-related if there was a known infectious cause [3]. Remaining NADCs were considered noninfection-related. Additionally, to align with consensus recommendations and explore the role of tumor immunogenicity, posthoc classifications were performed by pooling virus-associated cancers (ADCs and infection-related NADCs) [27], and by stratifying noninfection-related NADCs into immunologically “hot” and “cold” phenotypes (susceptible or nonsusceptible to immune checkpoint therapies) [41–43] based on the most prevalent histological type per organ site. Individual cancers with ≥ 10 events were highlighted to provide contemporary incidence estimates; rarer cancers (< 10 events) are detailed in Supplemental Table S1, <https://links.lww.com/QAD/D973>.

Statistical analyses

Baseline characteristics were summarized using means (SD), medians (Q1, Q3), or counts (%) and compared between those developed cancer vs. those who did not. Similar descriptive analyses were also generated for the most common cancers. Incidence rates per 1000 person-years was calculated for the total cohort and stratified by natal sex and GBD region. Additionally, the incidence rates of the most common cancers were also estimated and visualized using forest plots.

Cause-specific Cox proportional hazard regression analysis was used to estimate the effect of risk factors on the hazard of a new cancer event. We started with an unadjusted analysis by including risk factors individually as covariates in the model. Based on the findings of the univariate analyses, the contributions of combinations of risk factors were evaluated in a multivariable Cox regression model. The final model included the risk factors that were significantly related to new cancer events in the multivariate model above, and other factors reported in the literature. Baseline CD4 was selected over nadir CD4 due to collinearity and superior model fit (lower Akaike's Information Criterion). Age linearity was assessed via regression splines and likelihood ratio tests [44]. Two-way interactions between pitavastatin treatment and risk factors that are significantly related to cancer in the multivariate model were evaluated to assess for any potential effect modification by pitavastatin. Interaction terms between the CD4/CD8 ratio and indicators of data

availability were used to allow inclusion of participants with CD4/CD8 ratio unavailable through clinical care at REPRIEVE entry in all analyses.

Secondary outcomes followed similar modeling procedures. Sensitivity analysis was performed for the all cancers and noninfection-related NADCs by restricting events to those occurring one year after baseline, minimizing the effect of potentially undiagnosed cancers at baseline. To assess whether pooling virus-associated cancers or accounting for tumor immunogenicity altered the relationship with HIV-specific risk factors, we conducted posthoc sensitivity analyses for these cancer types. Due to sparse data, only unadjusted models were performed for ADCs, infection-related NADCs, and “hot” tumor phenotypes. Estimated hazard ratios (HRs) are presented with 95% Wald CIs. There was no adjustment for multiplicity. The analyses used SAS version 9.4M7 (SAS Institute), on a Linux platform.

Results

Baseline characteristics of analysis population

The analysis included 7507 participants with no history of cancer at baseline and a median follow-up of 5.6 years (Q1–Q3: 4.6–6.3). Demographics and clinical characteristics of participants, stratified by whether they developed cancer and by cancer types, are summarized in Table 1 and Tables S2 and S3, Supplemental Digital Content, <https://links.lww.com/QAD/D973>. In the overall cohort, the median age was 50 years (Q1–Q3: 45–55) and 31% ($n = 2362$) were female at birth. Forty eight percent ($n = 3607$) were from LMICs: Latin American and Caribbean for 18% ($n = 1383$), Southeast and East Asia for 8% ($n = 580$), South Asia for 7% ($n = 504$), and sub-Saharan Africa for 15% ($n = 1140$). Female participation was significantly higher in LMICs (42.1%, $n = 1517$) than HICs (21.7%, $n = 845$). Among participants from HICs, 52% ($n = 2044$) reported White race and 41% ($n = 1603$) Black or African-American race. Of the participants, 25% ($n = 1867$) reported current cigarette smoking, 24% ($n = 1818$) reported former cigarette smoking, and 23% ($n = 1713$) had obesity. The median time since HIV diagnosis was 12 years (Q1–Q3: 7–19); and 22% ($n = 1641$) had a history of noncancer AIDS-defining event. The median CD4⁺ cell count was 622 (Q1–Q3: 449–828) cells/mm³, and 48% ($n = 3625$) had a nadir CD4⁺ cell count of < 200 cells/mm³. Eighty-eight percent ($n = 5048$) had HIV-1 RNA below quantification in participants with available data.

Number of new cancer events, by cancer type

During follow-up, 219 participants developed cancer (Table 1), primarily noninfection-related NADCs ($n = 131$, 60%), followed by infection-related NADCs ($n = 57$, 26%) and ADCs ($n = 24$, 11%). Seven cancer events (3%) could not be classified into the cancer type above due to

Table 1. Baseline HIV-related health status of participants with incident cancer vs. controls (no incident cancer), by cancer category.

		Full analysis Total	Controls (no *cancer) Pooled controls	Participants with ^a cancer				
				Pooled can- cer	ADC	Infection-related NADC	Noninfection- related NADC	Unspecified
No. of participants		7507	7288	219	24	57	131	7
Natal sex	Male	5145 (69%)	4985 (68%)	160 (73%)	17 (71%)	47 (82%)	92 (70%)	4 (57%)
	Female	2362 (31%)	2303 (32%)	59 (27%)	7 (29%)	10 (18%)	39 (30%)	3 (43%)
GBD super region	High Income	3900 (52%)	3748 (51%)	152 (69%)	13 (54%)	40 (70%)	94 (72%)	5 (71%)
	L. America	1383 (18%)	1355 (19%)	28 (13%)	6 (25%)	5 (9%)	16 (12%)	1 (14%)
	S.East/East Asia	580 (8%)	567 (8%)	13 (6%)	1 (4%)	3 (5%)	9 (7%)	0 (0%)
	South Asia	504 (7%)	497 (7%)	7 (3%)	2 (8%)	3 (5%)	2 (2%)	0 (0%)
	Sub-Saharan Africa	1140 (15%)	1121 (15%)	19 (9%)	2 (8%)	6 (11%)	10 (8%)	1 (14%)
	Age (years)	Median (Q1, Q3)	50 (45, 55)	50 (45, 55)	52 (48, 58)	49 (46, 55)	53 (48, 59)	53 (48, 58)
	40-49	3640 (48%)	3567 (49%)	73 (33%)	13 (54%)	16 (28%)	40 (31%)	4 (57%)
	50-59	3226 (43%)	3118 (43%)	108 (49%)	7 (29%)	28 (49%)	71 (54%)	2 (29%)
	60+	641 (9%)	603 (8%)	38 (17%)	4 (17%)	13 (23%)	20 (15%)	1 (14%)
Time since HIV diagnosis (years)	Median (Q1, Q3)	12 (7, 19)	12 (7, 19)	16 (9, 23)	12 (6, 21)	21 (13, 26)	16 (10, 23)	12 (9, 17)
Mode of HIV acquisition	# missing	4	4	0	0	0	0	0
	Heterosexual Contact	3872 (52%)	3781 (52%)	91 (42%)	10 (42%)	26 (46%)	52 (40%)	3 (43%)
	Homosexual Contact	2616 (35%)	2524 (35%)	92 (42%)	12 (50%)	23 (40%)	54 (41%)	3 (43%)
	Injection Drug Use	191 (3%)	182 (2%)	9 (4%)	0 (0%)	3 (5%)	6 (5%)	0 (0%)
	Multiple Modes	270 (4%)	264 (4%)	6 (3%)	1 (4%)	1 (2%)	4 (3%)	0 (0%)
	Other	97 (1%)	94 (1%)	3 (1%)	0 (0%)	0 (0%)	3 (2%)	0 (0%)
	Unknown	457 (6%)	439 (6%)	18 (8%)	1 (4%)	4 (7%)	12 (9%)	1 (14%)
	# missing	4	4	0	0	0	0	0
Nadir CD4 (cells/mm ³)	<50	1321 (18%)	1274 (17%)	47 (21%)	4 (17%)	16 (28%)	26 (20%)	1 (14%)
	50-199	2304 (31%)	2235 (31%)	69 (32%)	9 (38%)	22 (39%)	35 (27%)	3 (43%)
	200-349	1998 (27%)	1943 (27%)	55 (25%)	7 (29%)	8 (14%)	39 (30%)	1 (14%)
	350+	1630 (22%)	1588 (22%)	42 (19%)	4 (17%)	10 (18%)	27 (21%)	1 (14%)
	Unknown	254 (3%)	248 (3%)	6 (3%)	0 (0%)	1 (2%)	4 (3%)	1 (14%)
History of AIDS-defining event		1641 (22%)	1595 (22%)	46 (21%)	7 (29%)	16 (28%)	20 (15%)	3 (43%)
CD4 ⁺ cell count (cells/mm ³)	Median (Q1, Q3)	622 (449, 828)	623 (450, 828)	609 (419, 819)	599 (491, 914)	521 (316, 722)	659 (474, 855)	529 (390, 1071)
	<350	1010 (13%)	972 (13%)	38 (17%)	3 (13%)	18 (32%)	16 (12%)	1 (14%)
	350-499	1384 (18%)	1348 (18%)	36 (16%)	4 (17%)	10 (18%)	21 (16%)	1 (14%)
	500+	5113 (68%)	4968 (68%)	145 (66%)	17 (71%)	29 (51%)	94 (72%)	5 (71%)
CD4/CD8 ratio	Median (Q1, Q3)	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (0, 1)	1 (0, 1)	1 (1, 1)	1 (0, 1)
	# missing	1221	1187	34	4	10	20	0
HIV-1 RNA (copies/ml)	<LLQ	5048 (88%)	4893 (88%)	155 (86%)	15 (83%)	35 (80%)	99 (88%)	6 (100%)
	LLQ -< 400	590 (10%)	572 (10%)	18 (10%)	3 (17%)	6 (14%)	9 (8%)	0 (0%)
	400+	123 (2%)	115 (2%)	8 (4%)	0 (0%)	3 (7%)	5 (4%)	0 (0%)
	# missing	1746	1708	38	6	13	18	1
BMI (race-specific)	Low/Normal	3072 (41%)	2977 (41%)	95 (43%)	6 (25%)	30 (53%)	55 (42%)	4 (57%)
	Overweight	2715 (36%)	2636 (36%)	79 (36%)	10 (42%)	17 (30%)	50 (38%)	2 (29%)
	Obese	1713 (23%)	1668 (23%)	45 (21%)	8 (33%)	10 (18%)	26 (20%)	1 (14%)
Smoking status	Current	1867 (25%)	1797 (25%)	70 (32%)	7 (29%)	20 (35%)	41 (31%)	2 (29%)
	Former	1818 (24%)	1756 (24%)	62 (28%)	8 (33%)	22 (39%)	30 (23%)	2 (29%)
	Never	3813 (51%)	3726 (51%)	87 (40%)	9 (38%)	15 (26%)	60 (46%)	3 (43%)
	# missing	9	9	0	0	0	0	0

^aIncident cancer is defined as newly diagnosed cancer while on REPRIEVE. One participant with a reported ADC had a subsequent NADC reported (noninfection-related), and is summarized in the ADC column.

Duration of HIV is defined as years since first positive HIV test. Mode of HIV acquisition is participant self-report of most likely mode of HIV acquisition. HIV-1 RNA was captured if available through standard of care. The assays used for testing varied, including assays with lower limits of quantitation (LLQ) between 20 and 400 copies/ml.

ADC, AIDS-defining cancer; NADC, non-AIDS-defining cancer; L. America, Latin America and Caribbean.

insufficient diagnostic information. One participant presented with two distinct malignancies; only the initial ADC was included to maintain analytical consistency. Among participants who developed cancer, 73% ($n=160$) were male sex at birth, and 31% ($n=67$) were from LMICs. The median times to cancer diagnosis were 3.1 years (Q1–Q3: 1.5–4.7) for all cancers, 2.0 years (Q1–Q3: 1.1–4.0) for ADCs, 2.9 years (Q1–Q3: 1.6–4.4) for infection-related NADCs, and 3.4 years (Q1–Q3: 1.6–4.9) for noninfection-related NADCs. The spectrum of individual malignancies by category is shown in Table S1, Supplemental Digital Content, <https://links.lww.com/QAD/D973>. Anal cancer ($n=18$, 32%), liver cancer ($n=12$, 21%), and oral cavity or pharyngeal cancer ($n=10$, 18%) were the most common infection-related NADCs. Of the liver cancer cases, 17% ($n=2$) had HBV infection, while none had HCV infection at baseline. The leading noninfection-related NADCs included prostate cancer ($n=36$, 27%), lung cancer ($n=19$, 15%), and breast cancer ($n=18$, 14%). Notably, 95% ($n=18$) of lung cancer occurred in participants with a history of cigarette smoking (13 current and 5 former smokers).

Incidences of cancer and cancer types, by sex and GBD region

Incidence rates for all cancers, cancer types, and the most common individual cancers for all participants, as well as by sex and GBD regions are shown in Figs. 1–3. The overall cancer incidence rate (IR) was 5.6 per 1000 person years (95% CI: 4.9–6.4), with noninfection-related NADCs (IR: 3.4, 95% CI: 2.8, 4.0) occurring more frequently than infection-related NADCs (IR: 1.5, 95% CI: 1.1, 1.9) and ADCs (IR: 0.6, 95% CI: 0.4, 0.9) (Fig. 1). Combining ADCs and infection-related NADCs, the

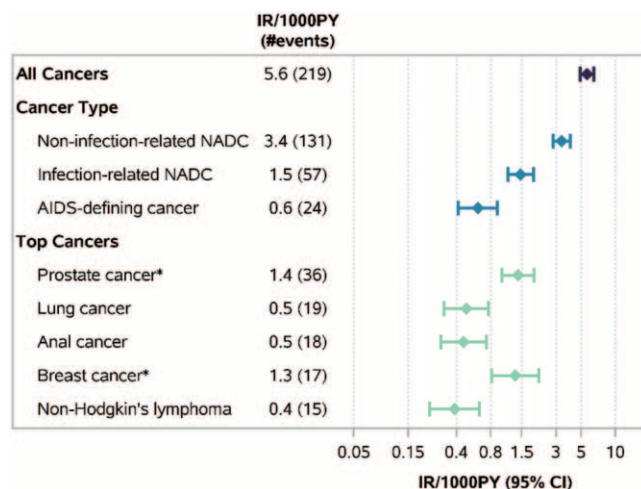


Fig. 1. Incidence rates of all cancers, and cancer types. PY: prostate (male*): 26 038.2 years; breast (female*): 12 973.6 years; other cancers: 39 011.8 years. Abbreviations: ADC, AIDS-defining cancer; NADC, non-AIDS-defining cancer; CI, confidence interval; PY, person years. * Restricted to male or female sex, as appropriate.

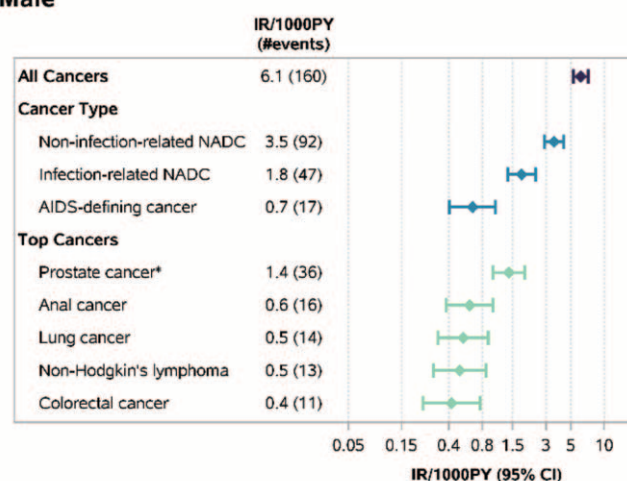
overall incidence of virus-associated cancers was 2.1 (95% CI: 1.7–2.6). The IRs among males were higher for all cancers (IR: 6.1, 95% CI: 5.3, 7.2) and for infection-related NADCs (IR: 1.8, 95% CI: 1.4, 2.4), compared to those among females (all cancers: IR: 4.5, 95% CI: 3.5, 5.9; infection-related NADCs: IR: 0.8, 95% CI: 0.4, 1.4) (Fig. 2, Figure S1, Supplemental Digital Content, <https://links.lww.com/QAD/D973>). Across GBD regions, participants from HICs had a higher incidence compared to those from LMICs for all cancers (HIC: IR: 7.6, 95% CI: 6.5, 9.0; LMIC: IR: 3.5, 95% CI: 2.8, 4.5), infection-related NADCs (HIC: IR: 2.0, 95% CI: 1.5, 2.7; LMIC: IR: 0.9, 95% CI: 0.6, 1.4), and noninfection-related NADCs (HIC: IR: 4.7, 95% CI: 3.9, 5.8; LMIC: IR: 1.9, 95% CI: 1.4, 2.7) (Fig. 3). Differences in overall cancer incidence rates across GBD regions outweighed within-region sex differences. While incidence fell substantially from HICs to LMICs for males (7.7 vs. 3.9) and females (7.4 vs. 3.0), absolute within-region sex differences remained comparatively modest in HICs (7.7 vs. 7.4) and in LMICs (3.9 vs. 3.0) (Figure S2, Supplemental Digital Content, <https://links.lww.com/QAD/D973>). Cumulative incidence curves for all cancers by GBD region are shown in Figure S3, Supplemental Digital Content, <https://links.lww.com/QAD/D973>.

Prostate cancer was the most common type of cancer in males (IR: 1.4, 95% CI: 1.0, 1.9, per 1000 person-years), while breast cancer was the most common type of cancer in females (IR: 1.3, 95% CI: 0.8, 2.1). The incidence of lung cancer was comparable between sexes, with IRs of 0.5 (95% CI: 0.3, 0.9) and 0.4 (95% CI: 0.2, 0.9) per 1000 person-years in males and females, respectively. Other leading cancer types included anal cancer in males (IR: 0.6, 95% CI: 0.4, 1.0) and invasive cervical cancer in females (IR: 0.4, 95% CI: 0.2, 0.9) (Fig. 2, Figure S1, Supplemental Digital Content, <https://links.lww.com/QAD/D973>). Different leading cancers were also observed across GBD regions (Fig. 3). The top three cancers in HICs were prostate cancer (IR: 2.0, 95% CI: 1.4, 2.9), lung cancer (IR: 0.9, 95% CI: 0.5, 1.4), and anal cancer (IR: 0.8, 95% CI: 0.5, 1.3). In contrast, the top three cancers in LMICs were breast cancer (IR: 1.2, 95% CI: 0.6, 2.2), colorectal cancer (IR: 0.3, 95% CI: 0.1, 0.7), and non-Hodgkin lymphoma (IR: 0.3, 95% CI: 0.1, 0.7). Breast cancer was the leading cancer among females in both HICs (IR: 1.5; 95% CI: 0.7–3.2) and LMICs (IR: 1.2; 95% CI: 0.6–2.2). Among males, the leading cancer was prostate cancer in HICs (IR: 2.0; 95% CI: 1.4–2.9) and non-Hodgkin lymphoma in LMICs (IR: 0.6; 95% CI: 0.3–1.2) (Figure S2, Supplemental Digital Content, <https://links.lww.com/QAD/D973>).

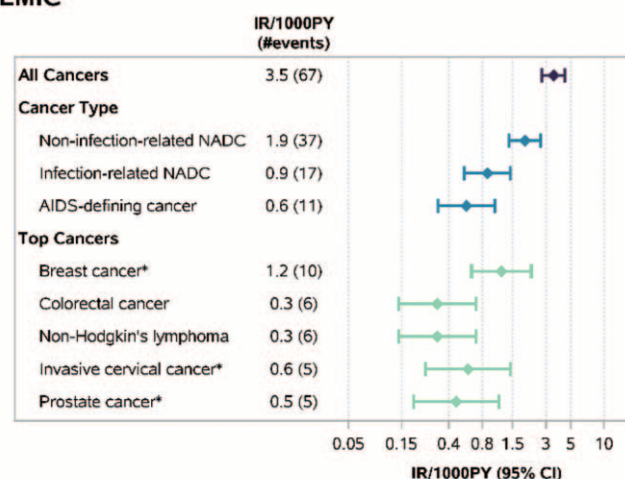
Risk factors associated with cancer

Univariable Cox regression models are shown in Fig. 4 and Figures S4–S9, Supplemental Digital Content, <https://links.lww.com/QAD/D973>. Higher age was associated with higher hazard of any cancer event and

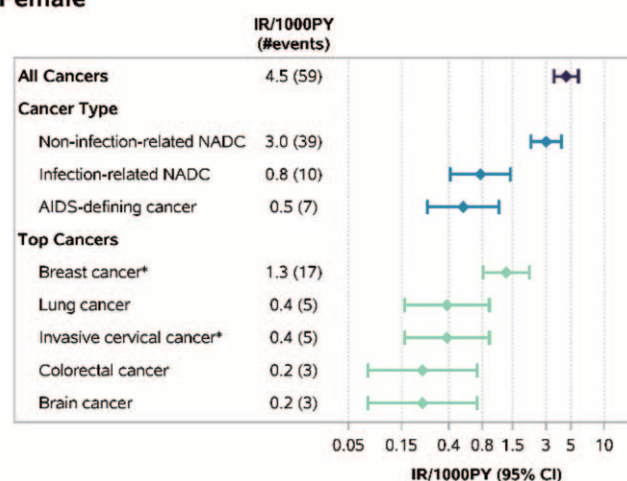
Male



LMIC



Female



HIC

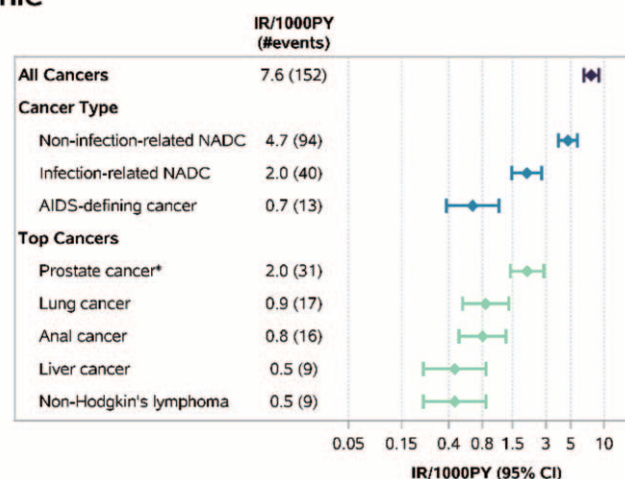


Fig. 2. Incidence rates of all cancers, and cancer types by sex. PY: male: 26 038.2 years; female: 12 973.6 years. ADC, AIDS-defining cancer; NADC, non-AIDS-defining cancer; CI, confidence interval; PY, person years. * Restricted to male or female sex, as appropriate. Rates based on small number of events (≤ 3) are statistically unstable and should be interpreted with caution.

all types except ADCs. Female sex was associated with decreased risk of any cancer, infection-related NADCs, and virus-associated cancers. Cigarettes smoking was associated with increased risk of any cancer and all types of cancer, except ADCs and noninfection-related NADCs. Among HIV-related risk factors, lower CD4 count was associated with increased risk of infection-related NADCs and virus-associated cancers.

In fully adjusted models, older age increased hazard for any cancer, noninfection-related NADCs, and virus-associated cancers, while LMICs residence was associated with a reduced hazard of any cancer and noninfection-related NADCs (Fig. 4, Figures S6 and S7, Supplemental Digital Content, <https://links.lww.com/QAD/D973>).

Fig. 3. Incidence rates of all cancers, and cancer types by GBD regions. PY: LMIC prostate (male*): 10 717.9 years; LMIC breast (female*): 8409.1 years; LMIC other cancers: 19 127.0 years; HIC prostate (male*): 15 320.3 years; HIC breast (female*): 4564.4 years; HIC other cancers: 19 884.8 years. ADC, AIDS-defining cancer; NADC, non-AIDS-defining cancer; HIC, high-income countries; LMIC, low- or middle-income countries; GBD, global burden of disease; CI, confidence interval; PY, person years. * Restricted to male or female sex, as appropriate.

Current smoking associated with higher risk of any cancer and virus-associated cancers, compared to never-smokers (Fig. 4, Supplemental Figure S6, <https://links.lww.com/QAD/D973>). Baseline CD4⁺ cell count, CD4/CD8 ratio, sex, or BMI showed no independent associations with the hazard of any cancer or specific cancer types in this population. Pitavastatin did not modify the associations between age, region, or smoking and cancer outcomes (Table S4, Supplemental Digital Content, <https://links.lww.com/QAD/D973>). One-year lag sensitivity analyses yielded consistent results (data not shown).

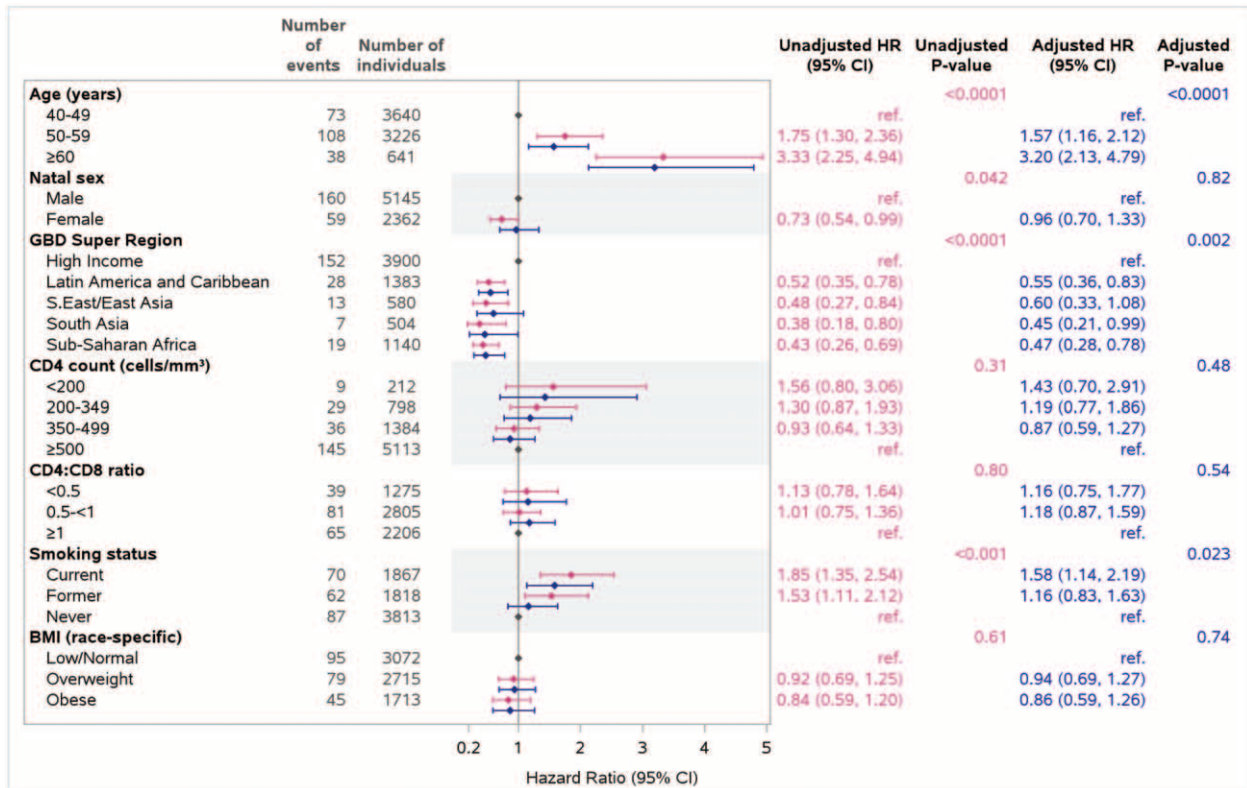


Fig. 4. Effects of baseline risk factors on any cancer. Effects of baseline risk factors on all cancers. Each factor is included in separate cause-specific Cox proportional hazards models (pink upper, lighter bar). Noncancer death is treated as competing events. The adjusted model (blue lower, darker bar) includes all specified risk factors. Abbreviations: NADCs, non-AIDS-defining cancers; BMI, body mass index; GBD, global burden of disease; HR, hazard ratio; LLQ, lower limit of quantification; ref, reference; CI, confidence interval.

Discussion

In a global cohort of PWH receiving effective ART, we report incidence rates of cancer overall and by cancer types in the context of modern ART. We found that cancer is an important comorbidity, with incidence varying by GBD and population characteristics. Non-infection-related NADCs were consistently identified as the most common cancer type overall and across sex and GBD regions. A wide range of cancers were observed, with prostate and breast cancers being the most frequent cancers overall and among males and females, respectively. Furthermore, higher age, residency in high-income GBD regions, and modifiable risk factor of cigarette smoking were associated with increased cancer risk in an ART well treated population.

The cancer incidence rate of 5.6 per 1000 person-years reinforces prior evidence that PWH face higher cancer risk than the general population [45–47]. While incidence rates are not directly comparable due to differences in age distribution and methodology, the International Agency for Research on Cancer estimated a global age-standardized incidence rate of 2.0 per 1000 person-years in 2022 [45]. Beyond the anticipated increased risk of ADCs, our findings confirm that both infection-related

and noninfection-related NADCs remain elevated among PWH [45,48]. These results suggested that stable ART does not fully mitigate cancer risk [1,3,49], potentially due to chronic inflammation or higher prevalence of traditional risk factors such as smoking.

Noninfection-related NADCs were the most common cancers in our study, while ADCs had the lowest incidence rate. This pattern was consistent across GBD regions and likely reflects stable ART restoring immune function in the vast majority of REPRIEVE participants [31,50]. Our findings agree with studies from the United States, Australia, and Europe showing that NADC incidence surpassed ADC after ART became widely available [5,16–18]. Importantly, our findings in the mid-low-income region provide evidence for the anticipated shift toward NADCs as efficient and timely ART therapy has become increasingly available. The low incidence of ADCs may also reflect REPRIEVE eligibility criteria, which required ≥180 days of stable ART and excluded individuals with a history of cancer. A prior study of the timing of cancer following initiation of ART revealed that the rates of ADCs peaks within the first six months after initiation of ART [12]. It is therefore possible that trial eligibility criteria likely reduced observed ADC rates, leading to a higher proportion of NADCs.

Cancer incidence in HICs was more than two-fold higher than in LMICs, driven primarily by both infection-related and noninfection-related NADCs. Notably, the differences in overall cancer incidence across GBD regions heavily outweighed within-region sex differences, which remained comparatively modest. These findings were likely attributable to industrialization-associated environmental risks and increased surveillance, diagnosis, and healthcare access [51,52], alongside aging and prolonged history of HIV infection [21,53] in HICs. Conversely, invasive cervical cancer and non-Hodgkin lymphoma were among the most common specific cancers in LMICs. The findings were in agreement with previous studies [54–60] and may be related to suboptimal HPV vaccination, inadequate screening or precancerous lesion treatment, delayed ART access, and diagnostic challenges. Further research in representative populations is warranted to investigate the factors underlying the regional difference.

While crude cancer incidence was higher in males, primarily driven by infection-related NADCs, sex was not a significant risk factor in multivariable adjusted models. This attenuation may be explained by the higher proportion of female participants from LMICs and their lower smoking prevalence. This parity in cancer risk differs from the patterns in the general population, where cancer risk is higher in men than women [61]. These findings suggest that HIV-associated immune dysregulation may act as a biological “equalizer” and highlights the importance of timely ART initiation and comprehensive cancer prevention for all PWH, including screening, vaccination, and smoking cessation.

Consistent with previous studies, older age was a major risk factor for all cancers and noninfection-related NADCs. PWH experience HIV-associated “premature aging” driven by mitochondrial dysfunction and cellular senescence [62]. These findings support the importance of age-appropriate surveillance and suggest that tailored screening guidelines, potentially involving earlier initiation or increased frequency, are required to optimize benefit and harm for aging PWH.

In this study, cigarette smoking was a prominent modifiable risk factor for cancer, which is in line with evidence that smoking prevention was associated with 24% reduction of NADCs among PWH [22]. The detrimental effects of smoking in PWH are amplified by high smoking prevalence across all income regions [63–65]. This risk is further compounded by evidence that smoking compromises ART response and exacerbates HIV-related chronic inflammation [23,66]. Additionally, in the REPRIEVE cohort, smoking was correlated with other risk factors, including substance use and higher rates of oncogenic virus infection. Notably, 74% of infection-related NADCs and 70% of virus-associated cancers occurred in current or former smokers. These observations underscore the critical need for integrated care

models that prioritize smoking cessation and lifestyle interventions for PWH.

No independent associations were observed between overall cancer, virus-associated cancers, or immunologically “hot” tumors and baseline HIV-specific risk factors, including absolute CD4 count or CD4/CD8 ratio. In the context of the REPRIEVE cohort's robust immune reconstitution (median CD4: 609 cells/mm³; median CD4/CD8 ratio: 1; 98% virally suppressed), traditional noncommunicable risk factors such as age and smoking may exert a more substantial influence on cancer risk. Our findings stand in contrast to the landmark NA-ACCORD study [36], which demonstrated that a lower CD4/CD8 ratio was a robust, independent predictor of subsequent infection-related cancers and immunologically “hot” noninfection-related tumors (such as lung cancer), while showing no relationship with immunologically “cold” tumors. The divergence is likely driven by fundamental cohort differences and limited statistical power. While NA-ACCORD captured historical registry data dated back to 1998, including individuals with severe immune inversion and long-term viral replication, REPRIEVE represents a relatively healthy, modern cohort on stable ART with restricted exposure variability. This lack of exposure variance, alongside few events ($n=29$ “hot” tumors), restricted the power to identify independent multivariable signals. Nevertheless, our unadjusted sensitivity analyses revealed directional trends for CD4/CD8 ratio that weakly mirror the findings by *Castilho et al.* Another plausible explanation is that HIV parameters were assessed at a single time point of trial entry. Studies employing dynamic, time-updated exposure metrics [28,36,67–69] are more likely to detect significant relationships than studies relying solely on baseline measurements [7,70–72].

Several limitations warrant consideration. The REPRIEVE cohort represents a relatively low-risk demographic with lower ASCVD risk [73,74] and smoking prevalence [64] than PWH in other cohort studies and in HIV primary care. The analysis was also constrained by a modest number of cancer events and a lack of central adjudication, though cancer was a prespecified prospective endpoint. Furthermore, the heterogeneity of NADCs and small numbers of specific cancers may limit ascertainment of the relationship between risk factors and these particular cancers. Finally, many cancers have long latency periods, which could impact our conclusions. To mitigate the possibility of including undiagnosed individuals at baseline, a sensitivity analysis excluding cases within the first year of follow-up was conducted, yielding results consistent with the primary findings. Nonetheless, with a median follow-up of 5.6 years, the full burden of cancers with longer latency periods may not yet be fully apparent.

Despite these limitations, this study provides critical data on cancer incidence, a prespecified secondary endpoint, in a modern, global clinical trial population receiving stable

ART. Our findings confirm a high cancer incidence in PWH well treated with ART, with the majority of events being noninfection-related NADCs. This work augments existing large-scale, multicontinent cancer registry data by providing insights into a population that maintained viral suppression across both HICs and LMICs. Furthermore, our study's capture of all cancer types is particularly valuable for LMICs where comprehensive, population-based cancer registries are often lacking. While consistent ART remains fundamental, our data highlight important opportunities to reduce cancer in PWH through smoking cessation and other targeted preventive and treatment strategies including vaccination, cancer screening, and treatment of precancerous lesions, even in younger PWH who currently are not the focus of such strategies.

Data sharing statement

Data are available from the REPRIEVE Trial (mghreprievetrial@mgb.org) upon reasonable request. In this case, shared data may include individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices). To gain access, data requestors will need to sign a data access agreement. Study protocol is available on clinicaltrials.gov. Data will be available following publication, pending approval by the parent study data sharing committee and the ACTG.

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NHLBI/NIH grants policy statement

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Conflicts of interest

S.Z. reports no disclosures.

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