Supplementary Material

CD4/CD8 ratio and cancer risk among adults with HIV

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Supplementary Table 1. The adjusted hazard ratio for lagged CD4/CD8 ratio and cancer risk[a]

Cancer event	CD4/CD8	Lagged 6 months HR (95%CI)	Lagged 12 months HR (95%CI)	Lagged 18 months HR (95%CI)	Lagged 24 months HR (95%CI)
Any Cancer[b]	0.30 vs. 0.80	1.24 (1.14-1.35)	1.31 (1.20-1.43)	1.24 (1.13-1.36)	1.23 (1.12-1.35)
	0.50 vs. 0.80	1.10 (1.06-1.14)	1.12 (1.08-1.17)	1.11 (1.06-1.15)	1.10 (1.06-1.15)
Non-Hodgkin lymphoma[b]	0.30 vs. 0.80	2.51 (1.82-3.47)	2.42 (1.72-3.39)	2.15 (1.50-3.09)	1.84 (1.27-2.66)
	0.50 vs. 0.80	1.53 (1.31-1.79)	1.44 (1.23-1.69)	1.42 (1.19-1.70)	1.34 (1.12-1.61)
Kaposi Sarcoma[b]	0.30 vs. 0.80	1.83 (1.26-2.64)	1.81 (1.25-2.63)	1.89 (1.27-2.82)	1.88 (1.27-2.79)
	0.50 vs. 0.80	1.35 (1.12-1.64)	1.28 (1.06-1.54)	1.36 (1.11-1.66)	1.31 (1.08-1.59)
Cervical Cancer[c]	0.30 vs. 0.80	1.09 (0.58-2.06)	1.48 (0.74-2.96)	1.06 (0.50-2.26)	0.67 (0.35-1.29)
	0.50 vs. 0.80	1.03 (0.69-1.54)	1.27 (0.81-1.97)	1.00 (0.62-1.61)	0.83 (0.55-1.25)
Lung Cancer[b]	0.30 vs. 0.80	1.66 (1.32-2.10)	1.60 (1.26-2.02)	1.6 (1.26-2.02)	1.61(1.25-2.07)
	0.50 vs. 0.80	1.28 (1.15-1.42)	1.28 (1.15-1.42)	1.28 (1.15-1.42)	1.29 (1.15-1.45)
Anal Cancer[b]	0.30 vs. 0.80	2.33 (1.71-3.18)	2.12 (1.55-2.91)	2.21 (1.59-3.06)	2.15 (1.53-3.02)
	0.50 vs. 0.80	1.54 (1.33-1.79)	1.43 (1.23-1.66)	1.47 (1.26-1.72)	1.46 (1.24-1.72)
Liver Cancer[d]	0.30 vs. 0.80	0.85 (0.61-1.17)	0.85 (0.60-1.19)	0.90 (0.64-1.27)	0.75 (0.52-1.06)
	0.50 vs. 0.80	0.94 (0.81-1.09)	0.95 (0.82-1.11)	0.99 (0.85-1.15)	0.91 (0.78-1.07)
Hodgkin Lymphoma	0.30 vs. 0.80	1.08 (0.67-1.73)	1.98 (1.19-3.30)	2.24 (1.33-3.76)	1.64 (0.95-2.83)
	0.50 vs. 0.80	1.03 (0.82-1.28)	1.40 (1.10-1.78)	1.39 (1.09-1.76)	1.31 (1.01-1.70)
Head and Neck Cancer[b]	0.30 vs. 0.80	1.10 (0.63-1.91)	1.13 (0.64-1.98)	1.19 (0.67-2.12)	1.24 (0.69-2.24)
	0.50 vs. 0.80	1.14 (0.88-1.46)	1.11 (0.86-1.42)	1.08 (0.84-1.40)	1.08 (0.83-1.40)
Prostate Cancer[e]	0.30 vs. 0.80	0.94 (0.75-1.17)	1.02 (0.82-1.28)	0.95 (0.75-1.20)	0.96 (0.75-1.22)
	0.50 vs. 0.80	0.96 (0.87-1.06)	0.98 (0.89-1.09)	0.97 (0.87-1.08)	0.96 (0.86-1.07)
Colorectal Cancer[b]	0.30 vs. 0.80	1.45 (0.93-2.27)	1.41 (0.89-2.22)	1.48 (0.93-2.35)	1.52 (0.94-2.46)
	0.50 vs. 0.80	1.25 (1.02-1.53)	1.21 (0.99-1.48)	1.27 (1.03-1.57)	1.30 (1.05-1.62)
Breast Cancer[c]	0.30 vs. 0.80	0.93 (0.54-1.60)	1.01 (0.58-1.75)	1.01 (0.57-1.79)	1.12 (0.62-2.02)
	0.50 vs. 0.80	1.09 (0.83-1.45)	1.13 (0.85-1.51)	1.13 (0.82-1.56)	1.11 (0.81-1.52)

[a]Adjusted Hazard Ratios and 95% confidence interval for different cancer were estimated using the multivariable Cox proportional

hazards models. HR: hazard ratio; CI: confidence interval

[b]Models for any cancer, lung cancer, Non-Hodgkin lymphoma, Kaposi sarcoma cancer, anal cancer, head and neck cancer, colorectal cancer included the covariates of age, sex, race and ethnicity, any history of chronic hepatitis C virus infection, year of cohort entry, and time-varying and time-updated CD4/CD8 ratio, CD4 cell count, HIV RNA, and history of AIDS-defining illness.

[c] Models for breast cancer and cervical cancer included only females and included age, race and ethnicity (White vs. non-White), and time-varying and time-updated CD4/CD8 ratio, CD4 cell count, HIV RNA, and history of AIDS-defining illness.

[d]The multivariable model for liver cancer included the covariates of age, sex, race and ethnicity, 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, year of cohort entry, and time-varying and time-updated CD4/CD8 ratio, CD4 cell count, HIV RNA, history of AIDS-defining illness, and history of cirrhosis.

[e]The multivariable model for prostate cancer included only males and covariates age, race and ethnicity, any history of chronic hepatitis C virus infection, and time-varying and time-updated CD4/CD8 ratio, CD4 cell count, HIV RNA, year of cohort entry, and history of AIDS-defining illness.

Supplementary Table 2. The adjusted hazard ratio for lagged CD4/CD8 ratio and cancer risk, restricted to person-time and laboratory results obtained after antiretroviral therapy initiation[a]

Cancer event	CD4/CD8	Lagged 6 months[b] HR (95%CI)	Lagged 12 months[c] HR (95%CI)
Any Cancer[d]	0.30 vs. 0.80	1.20 (1.09-1.31)	1.26 (1.15-1.39)
	0.50 vs. 0.80	1.09 (1.04-1.14)	1.11 (1.06-1.16)
Non-Hodgkin lymphoma[d]	0.30 vs. 0.80	2.40 (1.64-3.50)	2.51 (1.67-3.79)
	0.50 vs. 0.80	1.53 (1.27-1.84)	1.50 (1.24-1.81)
Kaposi Sarcoma[d]	0.30 vs. 0.80	1.98 (1.21-3.27)	2.42 (1.47-3.99)
	0.50 vs. 0.80	1.40 (1.10-1.79)	1.47 (1.15-1.87)
Cervical Cancer[e]	0.30 vs. 0.80	0.98 (0.49-1.99)	1.35 (0.62-2.95)
	0.50 vs. 0.80	0.96 (0.61-1.50)	1.16 (0.70-1.93)
Lung Cancer[d]	0.30 vs. 0.80	1.72 (1.34-2.21)	1.68 (1.31-2.17)
	0.50 vs. 0.80	1.30 (1.15-1.46)	1.31 (1.16-1.47)
Anal Cancer[d]	0.30 vs. 0.80	2.22 (1.60-3.08)	2.08 (1.49-2.90)
	0.50 vs. 0.80	1.51 (1.29-1.77)	1.43 (1.22-1.68)
Liver Cancer[f]	0.30 vs. 0.80	0.83 (0.59-1.17)	0.84 (0.59-1.21)
	0.50 vs. 0.80	0.94 (0.80-1.09)	0.95 (0.81-1.12)
Hodgkin Lymphoma	0.30 vs. 0.80	0.93 (0.56-1.54)	1.56 (0.90-2.70)
	0.50 vs. 0.80	0.97 (0.76-1.23)	1.27 (0.98-1.65)
Head and Neck Cancer[d]	0.30 vs. 0.80	1.09 (0.61-1.95)	1.06 (0.59-1.92)
	0.50 vs. 0.80	1.13 (0.86-1.47)	1.08 (0.82-1.41)
Prostate Cancer[g]	0.30 vs. 0.80	0.90 (0.71-1.14)	0.93 (0.73-1.18)
	0.50 vs. 0.80	0.94 (0.84-1.09)	0.94 (0.84-1.05)
Colorectal Cancer[d]	0.30 vs. 0.80	1.72 (1.08-2.74)	1.39 (0.87-2.23)
	0.50 vs. 0.80	1.38 (1.10-1.73)	1.23 (0.98-1.54)
Breast Cancer[e]	0.30 vs. 0.80	1.00 (0.53-1.89)	1.19 (0.62-2.28)
	0.50 vs. 0.80	1.17 (0.85-1.62)	1.29 (0.92-1.82)

[a]Adjusted hazard ratios and 95% confidence interval for different cancer were estimated using the multivariable Cox proportional hazards models. HR: hazard ratio; CI: confidence interval.

[b] For models examining six-month lagged CD4/CD8 ratio values, 72,541 PWH contributed 452,665 person-years of observation and 4,287 incident cancer diagnoses.

[c]For models examining 12-month lagged CD4/CD8 ratio values, 70,005 PWH contributed 429,710 person-years of observation and 3,992 incident cancer diagnoses.

[d]Models for any cancer, lung cancer, non-Hodgkin lymphoma, Kaposi sarcoma cancer, anal cancer, head and neck cancer, colorectal cancer included the covariates of age, sex, race and

ethnicity, any history of chronic hepatitis C virus infection, year of cohort entry, and time-varying and time-updated CD4/CD8 ratio, CD4 cell count, HIV RNA, and history of AIDS-defining illness.

[e]Models for breast cancer and cervical cancer included only females and included age, race and ethnicity (White vs. non-White), and time-varying and time-updated CD4/CD8 ratio, CD4 cell count, HIV RNA, and history of AIDS-defining illness.
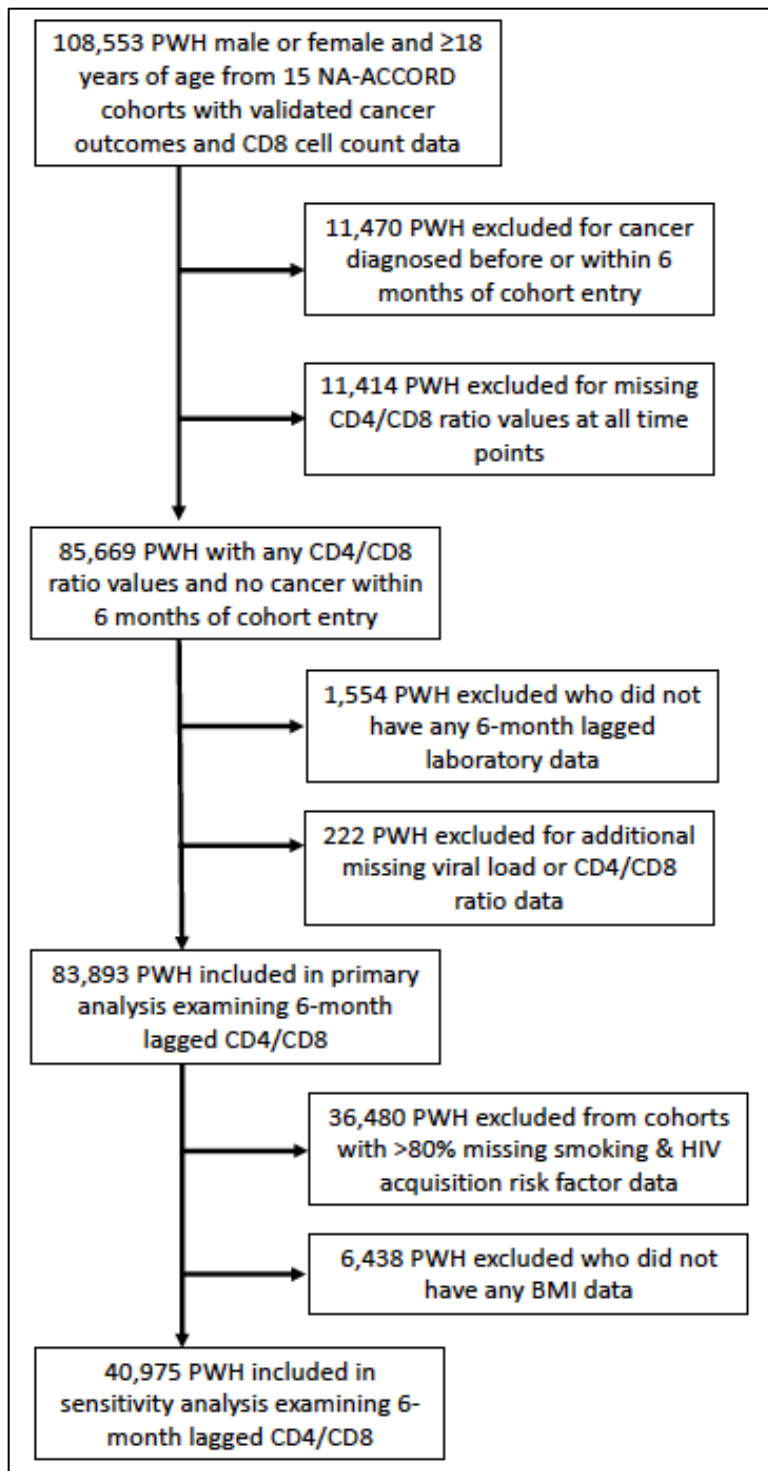
[f]The multivariable model for liver cancer included the covariates of age, sex, race and ethnicity, any history of chronic hepatitis C virus infection, history of chronic hepatitis B virus infection, history of heavy alcohol use, history of injection drug use, year of cohort entry, and time-varying and time-updated CD4/CD8 ratio, CD4 cell count, HIV RNA, history of AIDS-defining illness, and history of cirrhosis.

[g]The multivariable model for prostate cancer included only males and covariates age, race and ethnicity, any history of chronic hepatitis C virus infection, and time-varying and time-updated CD4/CD8 ratio, CD4 cell count, HIV RNA, year of cohort entry, and history of AIDS-defining illness.
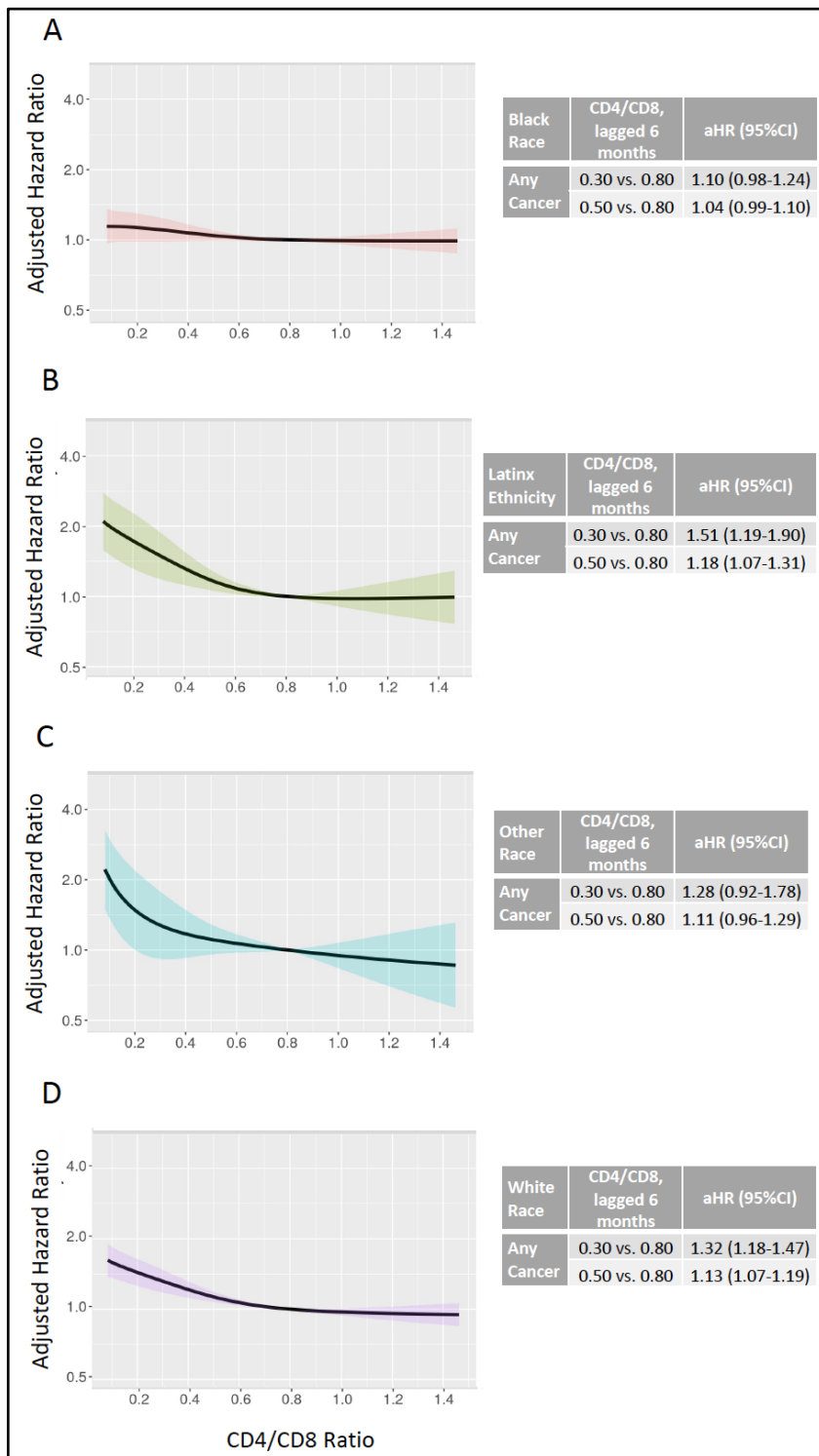
Supplementary Figures
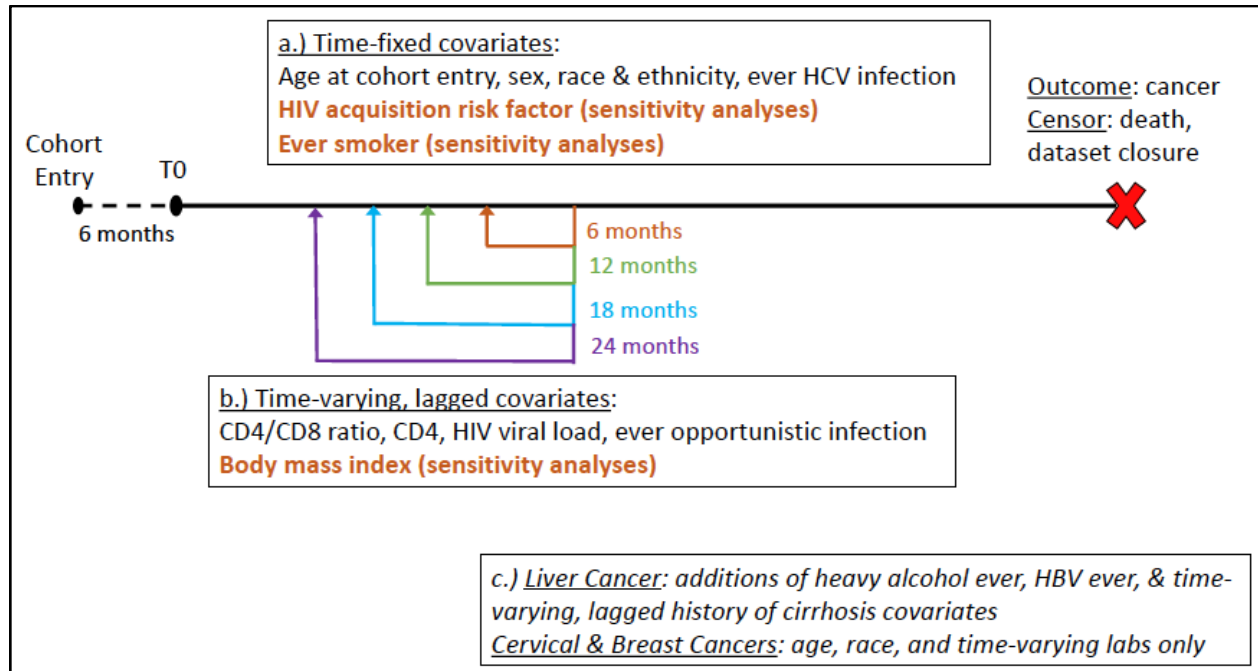
Supplementary Figure 1. Conceptual diagram of time-varying and time-fixed covariates used in multivariable, time-to-event analyses. Black line indicates observation time from T0 to cancer event or death. Box (a) includes list of time-fixed covariates included in all models (black) and additional covariates included in sensitivity analyses (orange, bold). Box (b) lists the time-varying covariates included in all models (black) and added in sensitivity models (orange, bold). Time-varying covariates were lagged such that values referenced at a given point in during observation corresponded to recorded laboratory values or prevalent diagnoses (in the case of opportunistic infections) six (orange), twelve (green), eighteen (blue), and twenty-four (purple) months prior. Box (c) indicates additional time-fixed and time-varying covariates included in models for liver cancer and restricted list of covariates included in models for cervical and breast cancers.

Supplementary Figure 2. Study population flow chart. PWH: people living with HIV. BMI: body mass index.

A

Black Race	CD4/CD8, lagged 6 months	aHR (95%CI)
Any Cancer	0.30 vs. 0.80	1.10 (0.98-1.24)
	0.50 vs. 0.80	1.04 (0.99-1.10)

B

Latinx Ethnicity	CD4/CD8, lagged 6 months	aHR (95%CI)
Any Cancer	0.30 vs. 0.80	1.51 (1.19-1.90)
	0.50 vs. 0.80	1.18 (1.07-1.31)

C

Other Race	CD4/CD8, lagged 6 months	aHR (95%CI)
Any Cancer	0.30 vs. 0.80	1.28 (0.92-1.78)
	0.50 vs. 0.80	1.11 (0.96-1.29)

D

White Race	CD4/CD8, lagged 6 months	aHR (95%CI)
Any Cancer	0.30 vs. 0.80	1.32 (1.18-1.47)
	0.50 vs. 0.80	1.13 (1.07-1.19)

Supplementary Figure 3. Adjusted hazard ratio for CD4/CD8 ratio values lagged six months for any cancer by race and ethnicity: (A) Black race, (B) Latinx ethnicity, (C) Other and/or unknown

race and ethnicity, and (D) White race. Other Race and ethnicity included Asian, Indigenous, Multiracial, Other, and unknown race. Model 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 as well as an interaction term for CD4/CD8 ratio and race and ethnicity. aHR: adjusted hazard ratio; CI: confidence interval.
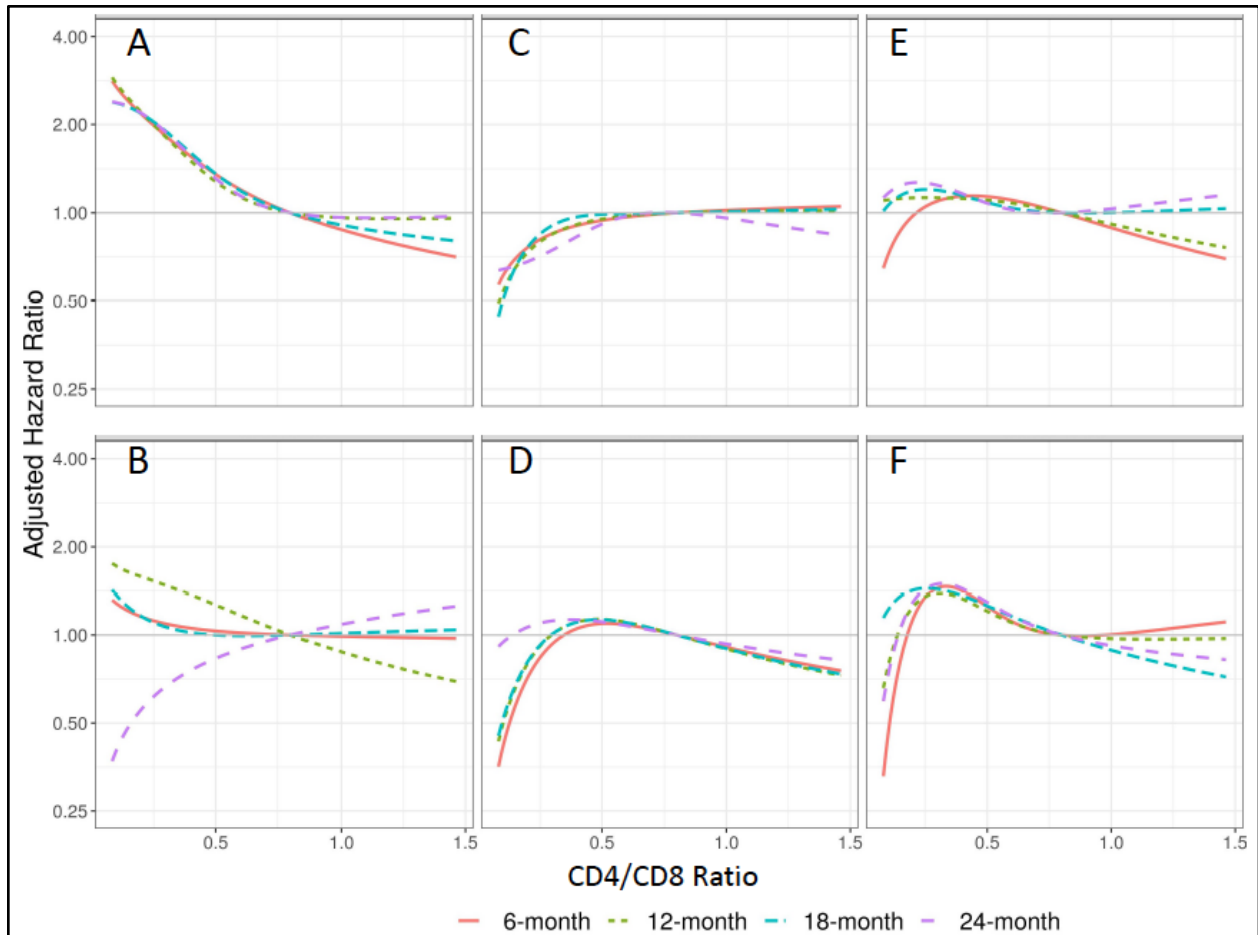
Supplementary Figure 4. Adjusted hazard ratio for cancer risk and CD4/CD8 ratios lagged six, twelve, 18, and 24-months. Adjusted hazard ratio for CD4/CD8 ratio values lagged six months (solid orange lines), 12 months (dashed green lines), 18 months (dashed teal lines), and 24 months (dashed purple lines) for the following cancers (number of events for each model): (A) Kaposi sarcoma (six months n=401; 12 months n=346; 18 months n=298; 24 months n=289); (B) Cervical cancer (six months n=43; 12 months n=42; 18 months n=31; 24 months n=27); (C) Liver cancer (six months n=310; 12 months n=286; 18 months n=286; 24 months n=268); (D) Breast cancer (six months n=65; 12 months n=62; 18 months n=54; 24 months n=50); (E) Head and neck cancer (six months n=120; 12 months n=117; 18 months n=113; 24 months n=105); (F) Colorectal cancer (six months n=199; 12 months n=186; 18 months n=181; 24 months n=171).

Models for Kaposi sarcoma, liver cancer, and head and neck 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 lagged CD4/CD8 ratio, CD4 cell count, HIV RNA, and history of AIDS-defining illness. Liver cancer models additionally included history of hepatitis B virus, any history of heavy alcohol use, history of injection drug use, and time-updated, lagged history of cirrhosis. Models for breast cancer and cervical cancer restricted to females only and included age, race and ethnicity (White vs. non-White), and time-varying and lagged CD4/CD8 ratio, CD4 cell count, HIV RNA, and history of AIDS-defining illness only due to small sample size.
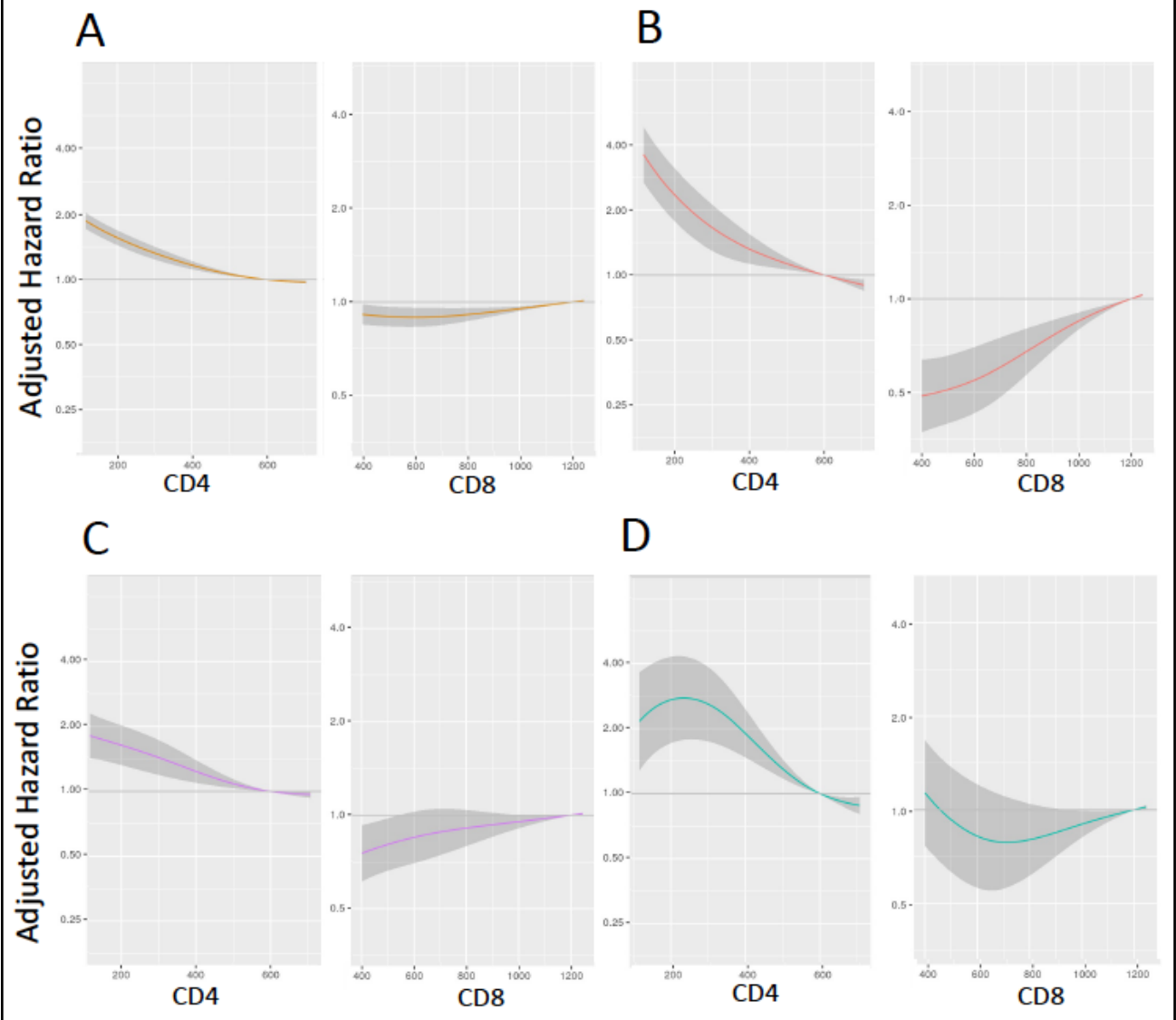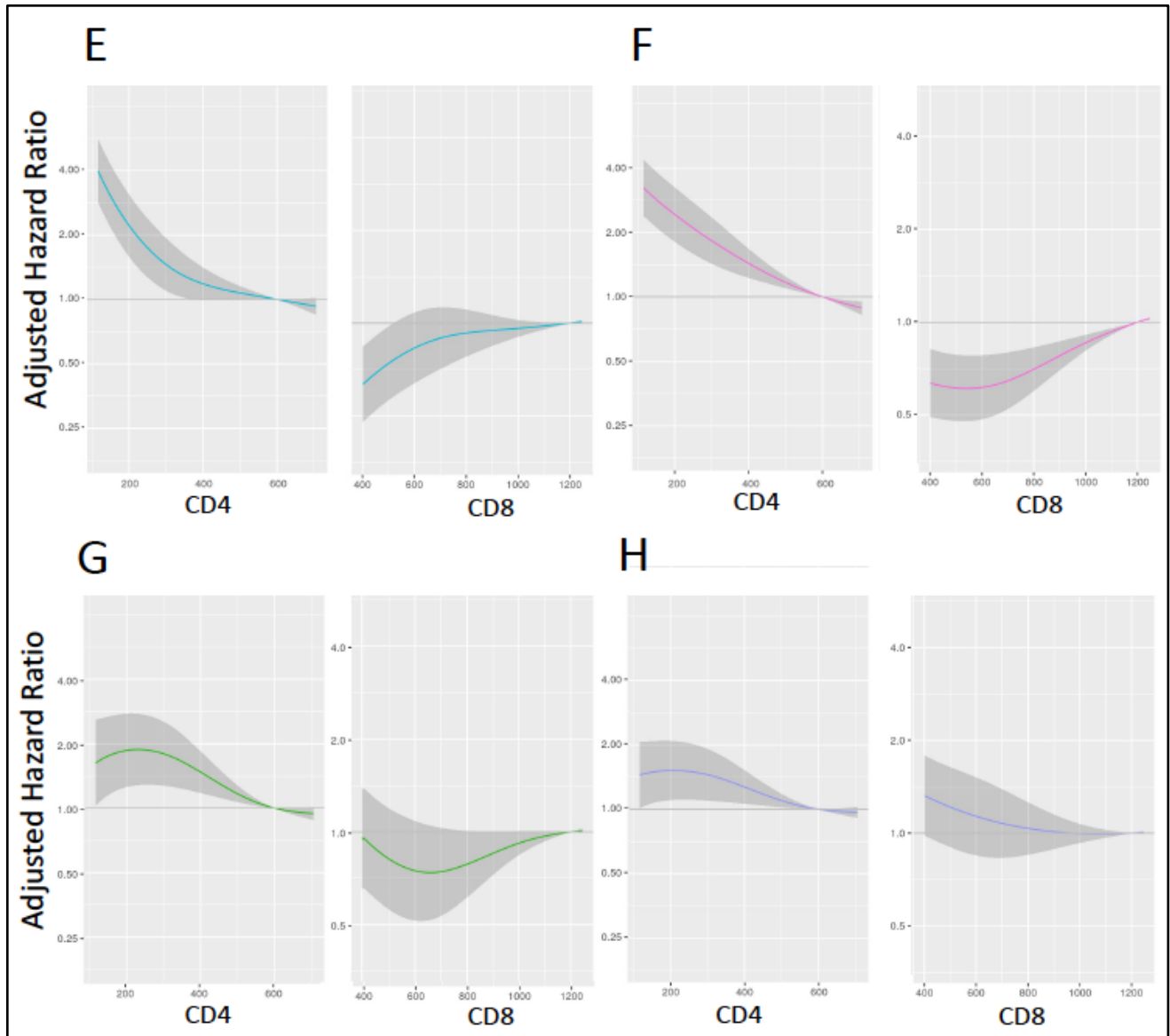
Supplementary Figure 5. Adjust hazard ratios for cancer risk predicted by six-month lagged absolute CD4 and CD8 cell counts.: (A) Any cancer, (B) Anal cancer, (C) Lung cancer, (D) Hodgkin lymphoma, (E) Kaposi sarcoma, (F) Non-Hodgkin lymphoma, (G) Colorectal cancer, and (H) Liver cancer. Models included the covariates of age, sex, race and ethnicity, year of cohort entry, any history of chronic hepatitis C virus infection, and time-varying and lagged CD8 cell count, CD4 cell count, HIV RNA, and history of AIDS-defining illness. Liver cancer models

additionally included history of hepatitis B virus, any history of heavy alcohol use, history of injection drug use, and time-updated, lagged history of cirrhosis.