Immunodeficiency and Cancer in 3.5 Million People Living with Human Immunodeficiency Virus: the South African HIV Cancer Match Study

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Summary: We studied the association between immunodeficiency and the incidence of various cancers in people living with the human immunodeficiency virus in South Africa. Lower CD4 cell counts were associated with a higher risk of multiple types of infection-related cancers.

Abstract

Background: We analysed associations between immunodeficiency and cancer incidence in a nationwide cohort of people living with the human immunodeficiency virus (HIV) in South Africa.

Methods: We used data from the South African HIV Cancer Match study built on HIV-related laboratory measurements from the National Health Laboratory Services and cancer records from the National Cancer Registry. We evaluated associations between time-updated CD4 cell count and cancer incidence rates using Cox proportional hazards models. We reported adjusted hazard ratios (aHR) over a grid of CD4 values and estimated the aHR per 100 CD4 cells/µl decrease.

Results: Of 3,532,266 people living with HIV (PLWH), 15,078 developed cancer. The most common cancers were cervical cancer (4,150 cases), Kaposi sarcoma (2,262 cases), and non-Hodgkin lymphoma (1,060 cases). The association between lower CD4 cell count and higher cancer incidence rates was strongest for conjunctival cancer (aHR per 100 CD4 cells/µl decrease: 1.46, 95% confidence interval [CI] 1.38-1.54), Kaposi sarcoma (aHR 1.23, 95% CI 1.20-1.26), and non-Hodgkin lymphoma (aHR 1.18, 95% CI 1.14-1.22). Among infection-unrelated cancers, lower CD4 cell counts were associated with higher incidence rates of oesophageal cancer (aHR 1.06, 95 CI 1.00-1.11), but not breast, lung, or prostate cancer.

Conclusions: Lower CD4 cell counts were associated with an increased risk of developing various infection-related cancers among PLWH. Reducing HIV-induced immunodeficiency may be a potent cancer prevention strategy among PLWH in sub-Saharan Africa, a region heavily burdened by cancers attributable to infections.

Keywords: HIV, cancer, immunodeficiency, CD4 cell count, South Africa

Introduction

The human immunodeficiency virus (HIV) has been classified as carcinogenic to humans by the International Agency for Research on Cancer [1]. Yet, the mechanisms through which HIV infection increases cancer risk are not fully understood. HIV-induced immunodeficiency and co-infections with oncogenic viruses among people living with HIV (PLWH) are likely to play a key role [2,3]. Evidence for direct pro-oncogenic effects of HIV, especially in lymphomagenesis, has also emerged [4].

Three infection-related cancers were found to occur particularly frequently among PLWH, namely Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and cervical cancer. Therefore, these malignancies were included in the case definition of the acquired immune deficiency syndrome (AIDS) [5]. However, over time it has become apparent that PLWH experience higher incidence rates of other non-AIDS-defining cancers, many of which are also infection-related [6–8]. For example, PLWH are at increased risk of developing Hodgkin's lymphoma (related to Epstein-Barr virus [EBV]), liver cancer (related to hepatitis B and C virus [HBV/HCV]), stomach cancer (related to helicobacter pylori [h.pylori]), and anogenital cancers (related to human papillomavirus [HPV]) compared with the general population [1,6–8]. Additionally, conjunctival squamous cell carcinoma is an emerging cancer among PLWH in Africa [9].

Immunodeficiency is a strong risk factor for developing KS and NHL [10,11]. KS and NHL incidence rates have steeply declined since antiretroviral therapy (ART) became widely available [12]. Advanced immunodeficiency has also been linked with increased rates of certain non-AIDS-defining cancers, such as Hodgkin's lymphoma, liver, lung, and anal cancer among PLWH in the US or Europe [10,11]. Studies of non-AIDS-defining cancers in sub-Saharan Africa are often limited by small numbers of incident cases.

We used data from the South African HIV Cancer Match (SAM) study to assess the association between lower CD4 cell counts and the risk of developing various cancer types among 3.5 million PLWH in South Africa.

Methods

The SAM study

The SAM study is a nationwide cohort of PLWH in South Africa and has been described in detail elsewhere [13]. Briefly, it is the result of a linkage between HIV-related laboratory records of the National Health Laboratory Services (NHLS) and pathology-based cancer diagnoses from the National Cancer Registry (NCR) for the period 2004-2014. The NHLS is the largest diagnostic pathology service in South Africa and is estimated to cover about 80% of the South African population (https://www.nhls.ac.za). Privacy-preserving probabilistic record linkage methods were used to identify NHLS records from the same individual and to link them to cancer diagnoses from the NCR [14]. The study received ethical approval from the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg (M190594), and the Cantonal Ethics committee in Bern (2016–00589).

Inclusion criteria and definitions

We included adults aged ≥18 years at cohort entry, with CD4 count measurements on separate days, and who had at least one year of follow-up after the date of their first CD4 count. PLWH entered the cohort at the time of the first HIV-related laboratory test (baseline). We excluded patients with missing information on sex or age. Individuals who were diagnosed with cancer before cohort entry were excluded from the analysis of that cancer.

We used the International Classification of Diseases, 10th Revision (ICD-10) diagnoses to identify cancer types. We categorized cancers into infection-related and infection-unrelated cancers, including breast cancer (C50), colorectal cancer (C18-C20), cancer of the connective and soft tissue

(C49), lung cancer (C34), melanoma of the skin (C43), oesophageal cancer (C15), and prostate cancer (C61). Infection-related cancers were further classified according to the infectious agent they are typically associated with (Table 1) [8]. Of note, we categorized conjunctival cancer as infection-related because HIV infection is an established risk factor [15], however, to date, an association with other oncogenic viruses remains unclear. We excluded basal cell carcinoma (C44.0) and squamous cell carcinoma of the skin (C44.1) from all analyses.

Statistical analysis

We produced descriptive statistics for PLWH with and without cancer. Age and calendar year were assessed at baseline. We defined time-at-risk as starting one year after the date of a patient's first CD4 measurement. We right-censored patients six months after their last HIV-related laboratory measurement, at the database closing date (January 1st 2015), or at the first diagnosis date of the cancer(s) under consideration, whichever came first. Thus, any patient with less than one year from the date of their first CD4 measurement to their right-censoring date was not included the analysis. We analysed associations between immunodeficiency (as indexed by time-updated CD4 count) and cancer incidence using proportional hazards (Cox) models separately for each cancer type/group. We time-updated CD4 counts at each measurement, carrying the value forward to the following CD4 measurement or censoring, whichever came first. We lagged the CD4 values by one year to minimize the risk of our results being affected by reverse causality; i.e., we modelled cancer incidence as a function of the CD4 count from one year before. We modelled time-updated CD4 count as a continuous variable and produced adjusted hazard ratio (aHR) curves with 95% confidence intervals (CIs) over a grid of CD4 values, for a reference of 200 cells/µl. We modelled the relationship between CD4 count and the log-hazard using penalized spline bases with three degrees of freedom [16]. All models were adjusted for sex, age (continuous variable with penalized splines), calendar year (time-updated, categorical: 2004-2007, 2008-2011, 2012-2014), and comorbidity (yes/no, time-updated) from cancers not part of the outcome of interest. The calendar period categories were chosen to

represent the changes in South African ART guidelines. In an additional analysis, we compared the relative strength of the CD4-cancer association across different cancers by estimating the aHR per 100 CD4 cells/µl decrease, assuming a linear relationship between CD4 count and the log-hazard. We performed this analysis including both sexes, and separately for men and women. We tested for interactions between sex and 100 CD4 count decrease. We assessed the Cox proportional hazards assumption using Schoenfeld residuals. We used the Akaike Information Criteria (AIC) to compare the model with penalized splines to the model without, i.e. the linear model. All analyses were done in Stata 15 (College Station, TX: StataCorp LLC) and R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Cancer cases and patient characteristics

The SAM cohort provided data on 13,608,064 PLWH, of which 3,532,266 were included in the overall cancer analysis (Supplementary Figure 1). A total of 27,954 adults were excluded from the analysis due to a prevalent cancer diagnosis (Supplementary Table 1). Among the included PLWH, 15,078 developed incident cancer over 9,108,565 person-years. The median time-at-risk was 2.1 years (inter-quartile range [IQR] 0.9-3.6) and the median number of CD4 measurements was 3 (IQR 2-5). Among infection-related cancers, the most common types were cervical cancer (4,150 cases), KS (1,262 cases), and NHL (1,060 cases). Non-AIDS-defining infection-related cancers were less common: there were 692 cases of non-AIDS-defining HPV-related cancers, 604 cases of conjunctival cancers, 288 cases of non-AIDS-defining EBV-related cancers, 164 cases of stomach cancers, 122 cases of bladder cancers, and 94 cases of liver and bile duct cancer.

There were 5,182 patients diagnosed with an infection-unrelated cancer. The most common infection-unrelated cancer was breast cancer (1,873 cases). There were 440 men diagnosed with prostate cancer. Lung cancer (415 cases), colorectal cancer (384 cases), oesophageal cancer (370

cases), melanoma of the skin (151 cases), and connective and soft tissue tumours (107 cases) were less common. Excluding these seven cancer types, there were 1,537 patients diagnosed with other infection-unrelated cancers.

Table 2 and Table 3 show the baseline characteristics of included PLWH, stratified by cancer type. Less than a third of the total study population were male (28.6%). Still, most patients with stomach, bladder, lung, and oesophageal cancer were male. The baseline median age was generally higher among PLWH with cancer compared to those remaining free of cancer. It ranged from 32.5 years for KS to 55.6 years for prostate cancer, compared to 33.7 years in PLWH without cancer. The median CD4 count at baseline was lower in PLWH who developed cancer than those who did not. It ranged from 179 cells/µL in PLWH with conjunctival cancer to 291 cells/µL in PLWH with breast cancer, compared to 292 cells/µL in PLWH free of cancer. A summary of age and calendar year at cancer diagnosis is shown in Supplementary Tables 2 and 3.

Immunodeficiency and cancer incidence

Across all cancers, the penalized spline approach yielded lower or similar AIC values compared to linear models, indicating better fit to the data (Supplementary Table 4). Thus, we chose this approach for our primary analysis.

From visual inspection of results, lower CD4 counts were associated with higher incidence rates of the three AIDS-defining cancers (Figure 1), the non-AIDS-defining HPV-related cancers, and conjunctival cancer (Figure 2), but not with higher rates of liver, stomach, or bladder cancer. There was no evidence of an association between lower CD4 counts and higher incidence of non-AIDS-defining EBV-related cancers (Hodgkin lymphoma and nasopharyngeal cancer). Among infection-unrelated cancers, we found an association between lower CD4 counts and higher incidence of connective and soft tissue cancer (Figure 3). There was also limited evidence of an association with oesophageal cancer and melanoma of the skin.

When assuming a linear relationship between CD4 count and the log-hazard, we found that among infection-related cancers, the association with CD4 count (aHR per 100 CD4 cells/µL decrease) was strongest for conjunctival cancer, followed by KS and NHL (Figure 4). Moreover, there was evidence for a weak protective effect of a lower CD4 count against stomach cancer (aHR per 100 CD4 cells/µL decrease 0.92, 95% CI 0.87-0.98). Among infection-unrelated cancers, the association between a lower CD4 count and cancer incidence was strongest for melanoma of the skin and oesophageal cancer. Sex modified the association between CD4 count and cancer incidence for NHL (p=0.006) and KS (p=0.005), with the association being more substantial in women than men (Supplementary Figure 2).

Discussion

Advanced immunodeficiency is associated with an increased risk of developing AIDS-defining cancers and various non-AIDS-defining infection-related cancers among a nationwide cohort of PLWH in South Africa. The association between lower CD4 counts and higher cancer incidence rates was strong for conjunctival cancer, KS, NHL, cervical and other HPV-related cancers. We did not find an association between lower CD4 counts and higher rates of cancers related to non-viral infections, i.e. stomach (h.pylori) and bladder cancer (schistosomiasis), and common infection-unrelated cancers including breast, lung, and prostate cancer. The association between lower CD4 counts and cancer incidence tended to be stronger in women than men for KS and NHL.

Since the start of the HIV epidemic, many studies have explored the relationship between immunodeficiency and the incidence of infection-related cancers. In line with these, we found a clear association between lower CD4 counts and increased rates of AIDS-defining cancers, i.e., KS [10,11,17,18], NHL [10,11,19,20], and cervical cancer [10,21]. We and others [10,11,22,23] also observed higher incidence rates of non-AIDS-defining HPV-related cancers such as anal [10,22], vaginal/vulvar [24], and head and neck squamous cell carcinoma [23] at lower CD4 counts. In our study, we assessed time-updated CD4 counts lagged by one year, whereas others identified nadir

and cumulative CD4 count as well as CD4 count lagged by several years to be stronger predictors for the risk of developing HPV-related cancers [10,22,23]. Immunodeficiency may promote HPV-related carcinogenesis early on by increasing the risk of HPV acquisition and reducing HPV clearance [25]. Our findings only partially confirm an increased liver cancer risk in PLWH with advanced immunodeficiency [10,11,26]. Conjunctival cancer is particularly common in Africa and has been linked to ultraviolet radiation and HIV infection [9]. Our results corroborate an important role of immunodeficiency in the development of this cancer. Studies from the US and Europe identified a clear association between lower recent CD4 counts and high Hodgkin's lymphoma incidence rates [10,11,27]. However, we did not find such a trend for EBV-related non-AIDS-defining cancers (Hodgkin's lymphoma and nasopharyngeal cancer). Misdiagnosis of HIV-associated lymphomas as tuberculosis (TB) is common in resource-limited settings with high TB prevalence [28], and this may have distorted the estimated association between immunodeficiency and Hodgkin's lymphoma risk. Of note, the association between CD4 counts and NHL risk in our study was also weaker than what has been described for North America and Europe [10,11,19]. Literature on the link between immunodeficiency and the risk of bladder and stomach cancers is scarce. An American study found a higher risk of developing non-cardia stomach cancer among PLWH with nadir CD4 counts ≤200 versus >200 cells/µl [29]. We did not find an association between lower CD4 counts and either bladder or stomach cancer incidence.

The association of lower CD4 counts with a KS and NHL risk was stronger among women than men. Most studies to date have not assessed whether the association between immunodeficiency and cancer risk is modified by sex. However, sex differences in cancer susceptibility have been reported consistently with most cancers occurring more frequently in men [30]. Sex differences in immune surveillance, with women generally mounting stronger immune responses, may contribute to differences in cancer susceptibility between male and female PLWH [31].

Few studies have assessed the association between HIV-induced immunodeficiency and infection-unrelated cancers, and data from Africa are generally not available. In the US, both breast and prostate cancer occur less frequently among PLWH than in the general population [32,33], with prostate cancer risk being reduced among men with lower CD4 counts at AIDS diagnosis [34]. However, we did not find an association between lower CD4 counts and either prostate or breast cancer incidence. In our study, there was some evidence for higher incidence rates at lower CD4 counts for oesophageal cancer as well as connective and soft tissue tumours. One study also found a higher risk of oesophageal squamous cell carcinoma among PLWH with lower nadir CD4, but the uncertainty was considerable [29]. The association between lower CD4 counts and the risk of connective and soft tissue tumours is in line with case reports suggesting an etiological role of EBV in the development of leiomyosarcomas and leiomyomas [35]. However, it could also be a spurious finding if some KS cases were misclassified as other soft tissue sarcomas. For malignant melanoma of the skin, we found a weak association with lower CD4 counts, but previous studies showed conflicting results [11,36]. The observation that some cancers currently categorized as infection-unrelated showed an association with lower CD4 counts could indicate that an unknown infectious cause may contribute to the development of these cancers.

This is the first large-scale study to explore associations between lower CD4 cell counts and various cancer types in sub-Saharan Africa. Our analysis included CD4 trajectories of 3.5 million PLWH over 9 million person-years. Our study has several limitations. Given that our cohort study was based on routine data, CD4 cell count measurements did not necessarily occur at regular intervals, and we did not have access to ART data. However, we adjusted for calendar period, with breakpoints chosen to match changes in South African ART guidelines. Information on cancer risk factors such as co-infections with other oncogenic viruses, lifestyle factors, or socioeconomic status was also unavailable. The database closing date was January 1st, 2015, but we do not expect immunodeficiency to influence cancer risk differently over time. The SAM study did not include mortality or emigration data. Thus, we censored patients six months after the last laboratory

measurement. While this limits the amount of follow-up data in our study, we do not expect it to have biased our results. CD4 count is a commonly-studied biomarker. Still, CD8 count, CD4/CD8 ratio, or RNA viral load are also important biomarkers for some cancers [10,37,38]. The NHLS does not routinely assess CD8 counts, and RNA viral loads were not reported frequently enough to create reliable trajectories.

Close to 30% of cancers in sub-Saharan Africa are infection-related [15]. Among PLWH the proportion of cancers attributable to infections is particularly high, with a proportion of 40% estimated in the US [8]. In sub-Saharan Africa, the proportion of infection-related cancers among PLWH is likely to be even higher. Reducing immunodeficiency through early detection of HIV and effective ART has been key in decreasing KS and NHL incidence among PLWH worldwide [12,39], and evidence is accumulating that timely initiation of ART might reduce the risk of developing cervical and anal cancers [40,41]. However, it is less clear whether reducing HIV-induced immunodeficiency has a preventive effect on other cancers. We have shown that lower CD4 counts are associated with higher rates of various infection-related and infection-unrelated cancers among PLWH in South Africa. Therefore, preventing HIV-induced immunodeficiency may be an important strategy to reduce the disproportionate cancer burden among PLWH in sub-Saharan Africa. As the effect of immunodeficiency on carcinogenesis varies by cancer types, in-depth cancer-specific analyses are required. The SAM study, with its nationwide cohort of PLWH, provides an ideal platform for such analyses.

In conclusion, lower CD4 counts are associated with an increased risk of developing various infection-related cancers among PLWH. Reducing HIV-induced immunodeficiency may be a potent cancer prevention strategy among PLWH in sub-Saharan Africa, a region heavily burdened by cancers attributable to infections.

NOTES:

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Conflicts of interest: No conflicts of interest to declare.

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Table 1: Categorisation of infection-related cancers.

Infection	Cancer	ICD-10 codes
	AIDS-defining cancers	
Human papillomavirus	Cervical	C53
Human herpesvirus 8	Kaposi sarcoma	C46
Epstein-Barr virus	Non-Hodgkin's lymphoma	C82-C85
	Non-AIDS-defining cancers	
Human papillomavirus	Anal	C21
	Head and neck	Various*
	Penile	C60
	Vaginal	C52
	Vulvar	C51
Epstein-Barr virus	Hodgkin lymphoma	C81
	Nasopharyngeal	C11
HIV**	Conjunctival	C69.0
Hepatitis B and C	Liver and bile duct	C22-24
Helicobacter pylori	Stomach	C16
Schistosomiasis	Bladder	C66, C67

* base of tongue (C01), lingual tonsil (C02.4), palatine tonsil (C09.0-09.9), oropharynx (C10.2-10.9), pharynx NOS (C14.0), Waldyer's ring (C14.2)

** HIV infection is an established risk factor for conjunctival cancer but an association with other oncogenic viruses remains controversial.

Table 2: Patient characteristics at the baseline test, stratified by the type of diagnosed cancer and infection group. HPV=human papillomavirus; IQR=inter-quartile range.

	AIDS-defining cancers			Non AIDS-defining cancers							
	Kaposi Sarcoma	**Invasive cervical cancer**	**Non-Hodgkin lymphoma**	**HPV-related** (Anal, head and neck, penile, vaginal, vulvar cancer)	**Epstein-Barr virus related** (Hodgkin lymphoma, nasopharyngeal cancer)	**Conjunctival cancer**	**Liver and bile duct cancer**	**Stomach cancer**	**Bladder cancer**	**Infection-unrelated** (see Table 3)	**Free of cancer**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
	2262	4150	1060	692	288	604	94	164	112	5182	3539516
Female	1256 (55.5)	4150 (100.0)	621 (58.6)	487 (70.4)	152 (52.8)	402 (66.6)	47 (50.0)	77 (47.0)	49 (43.8)	3381 (65.2)	2525784 (71.4)
Median age [IQR]	32.51 [27.37, 38.52]	38.62 [32.73, 45.77]	36.19 [30.25, 42.96]	36.64 [30.63, 45.10]	33.56 [28.04, 39.27]	35.14 [30.47, 40.80]	44.26 [35.02, 51.36]	45.04 [37.99, 53.86]	50.15 [41.24, 57.21]	44.79 [36.16, 52.68]	33.69 [27.58, 41.21]
Calendar period											
2004 - 2007	1116 (49.3)	1932 (46.6)	511 (48.2)	313 (45.2)	150 (52.1)	280 (46.4)	42 (44.7)	68 (41.5)	46 (41.1)	2388 (46.1)	752289 (21.3)
2008 - 2011	1025 (45.3)	1988 (47.9)	491 (46.3)	330 (47.7)	122 (42.4)	287 (47.5)	49 (52.1)	85 (51.8)	57 (50.9)	2491 (48.1)	2010765 (56.8)
2012 - 2014	121 (5.3)	230 (5.5)	58 (5.5)	49 (7.1)	16 (5.6)	37 (6.1)	3 (3.2)	11 (6.7)	9 (8.0)	303 (5.8)	776462 (21.9)
Median CD4 cell count [IQR]	256 [137, 389]	263 [139, 420]	221 [112, 355]	200 [105, 348]	253 [150, 422]	179 [87, 302]	219 [128, 380]	263 [155, 464]	289 [151, 425]	264 [139, 422]	291 [163, 452]
CD4 cell count											
< 50	168 (7.4)	267 (6.4)	81 (7.6)	58 (8.4)	15 (5.2)	60 (9.9)	10 (10.6)	16 (9.8)	8 (7.1)	327 (6.3)	200590 (5.7)

50-99	184 (8.1)	336 (8.1)	121 (11.4)	84 (12.1)	23 (8.0)	94 (15.6)	4 (4.3)	10 (6.1)	5 (4.5)	412 (8.0)	239861 (6.8)
100-199	386 (17.1)	740 (17.8)	226 (21.3)	156 (22.5)	50 (17.4)	136 (22.5)	22 (23.4)	25 (15.2)	22 (19.6)	961 (18.5)	589272 (16.6)
200-349	633 (28.0)	1011 (24.4)	258 (24.3)	150 (21.7)	73 (25.3)	143 (23.7)	24 (25.5)	42 (25.6)	27 (24.1)	1257 (24.2)	911713 (25.8)
350-499	355 (15.7)	630 (15.2)	134 (12.6)	81 (11.7)	45 (15.6)	61 (10.1)	12 (12.8)	20 (12.2)	20 (17.9)	788 (15.2)	634401 (17.9)
500-699	178 (7.9)	400 (9.6)	67 (6.3)	39 (5.6)	30 (10.4)	28 (4.6)	12 (12.8)	23 (14.0)	12 (10.7)	489 (9.4)	410855 (11.6)
≥ 700	79 (3.5)	208 (5.0)	40 (3.8)	28 (4.0)	12 (4.2)	9 (1.5)	1 (1.1)	9 (5.5)	4 (3.6)	281 (5.4)	228273 (6.4)
Missing	279 (12.3)	558 (13.4)	133 (12.5)	96 (13.9)	40 (13.9)	73 (12.1)	9 (9.6)	19 (11.6)	14 (12.5)	667 (12.9)	324551 (9.2)

Table 3: Patient characteristics at the baseline test, stratified by infection-unrelated cancer diagnosis. IQR=inter-quartile range.

	Breast cancer	Colorectal cancer	Connective tissue cancer	Lung cancer	Melanoma	Oesophagus cancer	Prostate cancer	Other infection-unrelated cancers*
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	1873	384	107	415	151	370	440	1537
Female	1850 (98.8)	223 (58.1)	59 (55.1)	117 (28.2)	89 (58.9)	166 (44.9)	0 (0.0)	923 (60.1)
Median age [IQR]	41.10 [34.18, 48.61]	45.18 [36.16, 53.18]	39.01 [31.22, 48.80]	49.19 [43.56, 55.11]	45.45 [37.55, 53.37]	48.99 [42.59, 55.13]	55.58 [50.46, 60.26]	43.53 [34.39, 51.70]
Calendar period								
2004 - 2007	896 (47.8)	159 (41.4)	55 (51.4)	183 (44.1)	67 (44.4)	175 (47.3)	173 (39.3)	726 (47.2)
2008 - 2011	886 (47.3)	194 (50.5)	47 (43.9)	198 (47.7)	77 (51.0)	173 (46.8)	235 (53.4)	721 (46.9)
2012 - 2014	91 (4.9)	31 (8.1)	5 (4.7)	34 (8.2)	7 (4.6)	22 (5.9)	32 (7.3)	90 (5.9)
Median CD4 cell count [IQR]	291 [165, 452]	259[155, 385]	248 [105, 430]	238 [124, 405]	233 [133, 374]	244 [121, 387]	244 [129, 401]	251 [131, 410]
CD4 cell count								
< 50	115 (6.1)	24 (6.2)	8 (7.5)	27 (6.5)	12 (7.9)	19 (5.1)	27 (6.1)	102 (6.6)
50-99	118 (6.3)	19 (4.9)	14 (13.1)	36 (8.7)	12 (7.9)	43 (11.6)	39 (8.9)	137 (8.9)
100-199	287 (15.3)	75 (19.5)	21 (19.6)	88 (21.2)	32 (21.2)	73 (19.7)	84 (19.1)	316 (20.6)
200-349	483 (25.8)	111 (28.9)	18 (16.8)	100 (24.1)	37 (24.5)	90 (24.3)	104 (23.6)	345 (22.4)
350-499	323 (17.2)	56 (14.6)	15 (14.0)	52 (12.5)	20 (13.2)	50 (13.5)	64 (14.5)	215 (14.0)
500-699	187 (10.0)	34 (8.9)	11 (10.3)	37 (8.9)	9 (6.0)	34 (9.2)	42 (9.5)	147 (9.6)
≥ 700	124 (6.6)	10 (2.6)	7 (6.5)	23 (5.5)	10 (6.6)	11 (3.0)	20 (4.5)	81 (5.3)
Missing	236 (12.6)	55 (14.3)	13 (12.1)	52 (12.5)	19 (12.6)	50 (13.5)	60 (13.6)	194 (12.6)

***** includes all infection-unrelated cancers not shown in the other columns

Figure legends

Figure 1: Adjusted hazard ratios (solid lines) with 95% confidence intervals (grey area) for the incidence of AIDS-defining cancers, comparing a grid of CD4 cell counts to the reference value of 200 cells/µL. The models are adjusted for sex, calendar year, and diagnosis of other cancers.

Figure 2: Adjusted hazard ratios (solid lines) with 95% confidence intervals (grey area) for the incidence of infection-related, non-AIDS-defining cancers, comparing a grid of CD4 cell counts to the reference value of 200 cells/µL. The models are adjusted for sex, calendar year, and diagnosis of other cancers. EBV=Epstein-Barr virus; HPV=human papillomavirus.

Figure 3: Adjusted hazard ratios (solid lines) with 95% confidence intervals (grey area) for the incidence of infection-unrelated cancers, comparing a grid of CD4 cell counts to the reference value of 200 cells/µL. The models are adjusted for sex, calendar year, and diagnosis of other cancers.

Figure 4: Adjusted hazard ratios for cancer incidence with associated 95% confidence intervals, per 100 decrease of CD4 cell count. The models assumed a linear relationship between CD4 cell count and the log-hazard of the cancer, while adjusting for sex, calendar year, and diagnosis of other cancers. The cancers are ranked in decreasing order of their adjusted hazard ratios. EBV=Epstein-Barr virus; HPV=human papillomavirus.

Figure 1

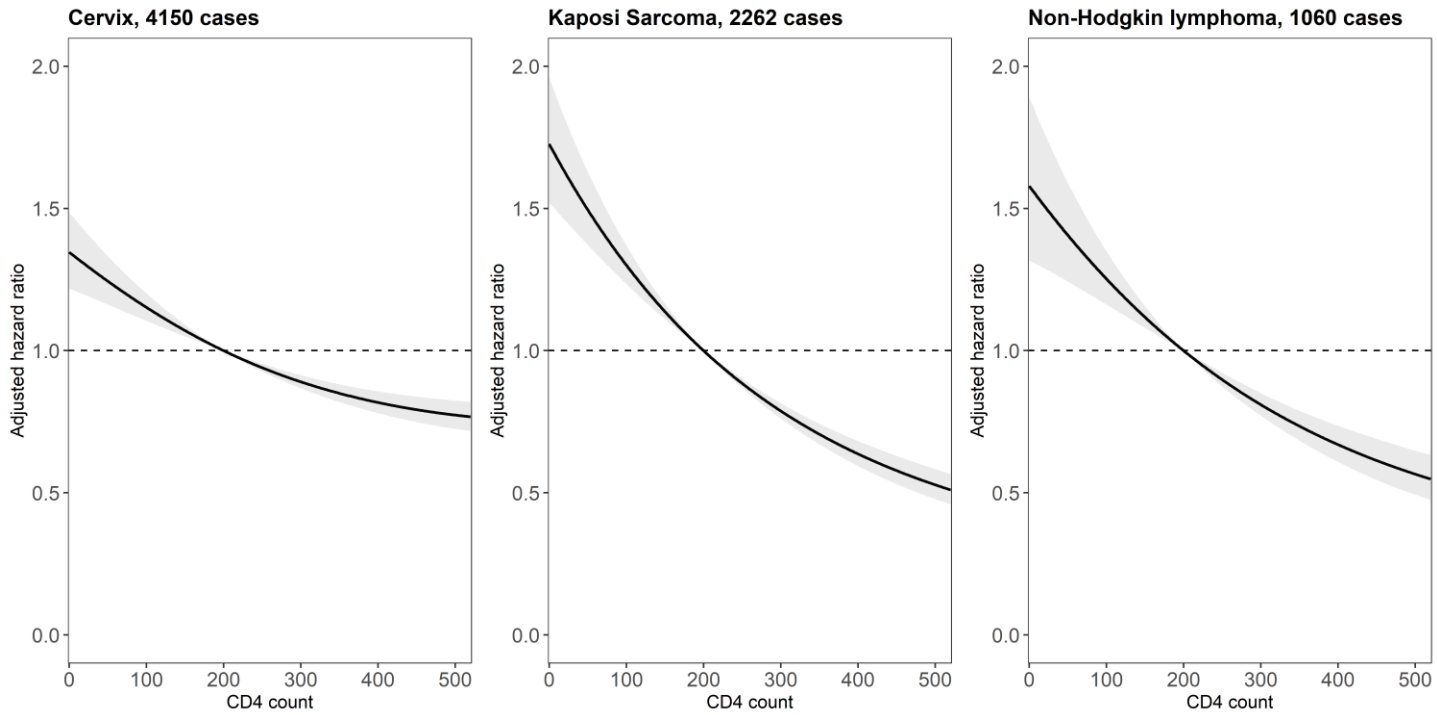

Figure 2

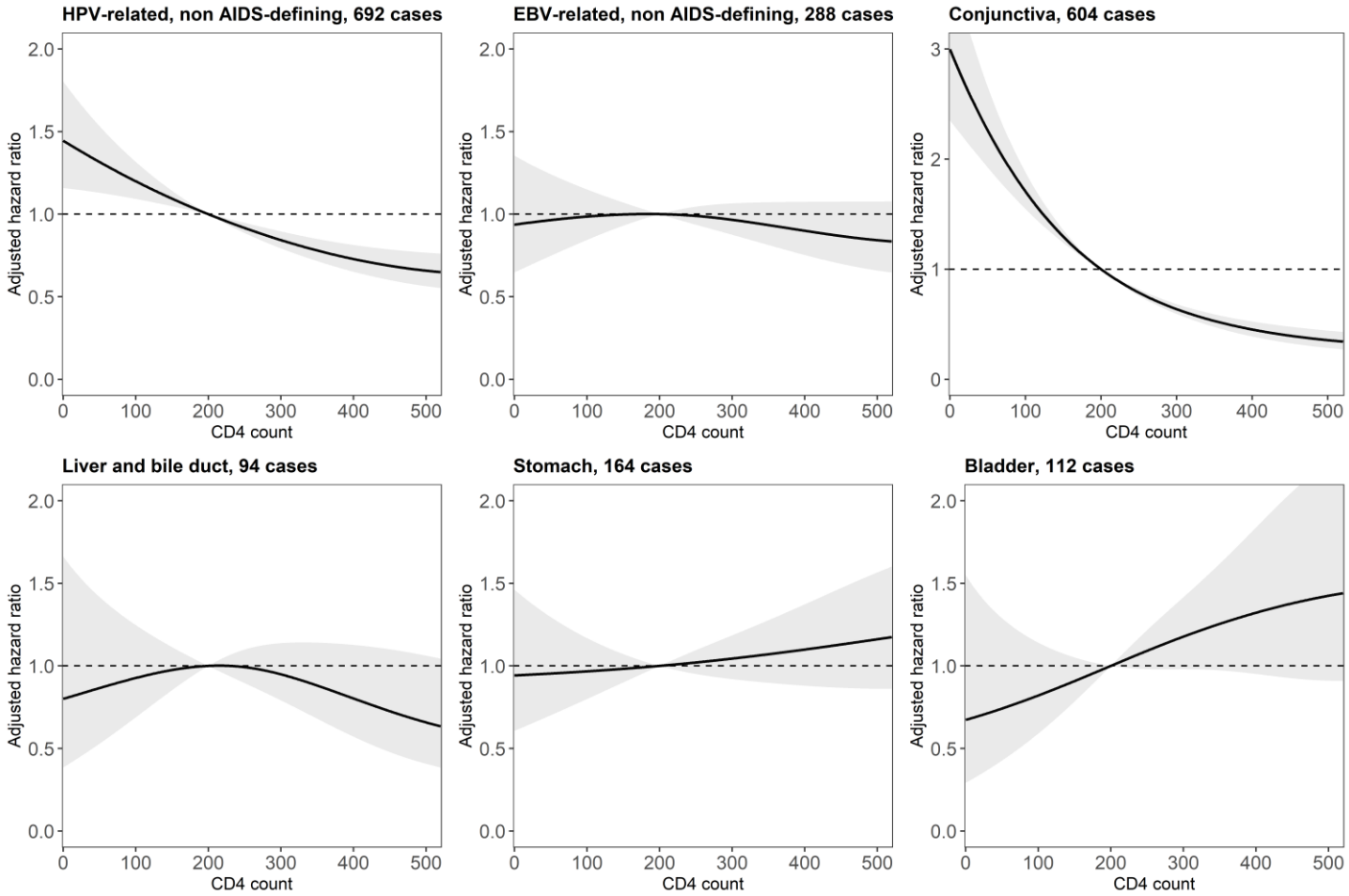

Figure 3

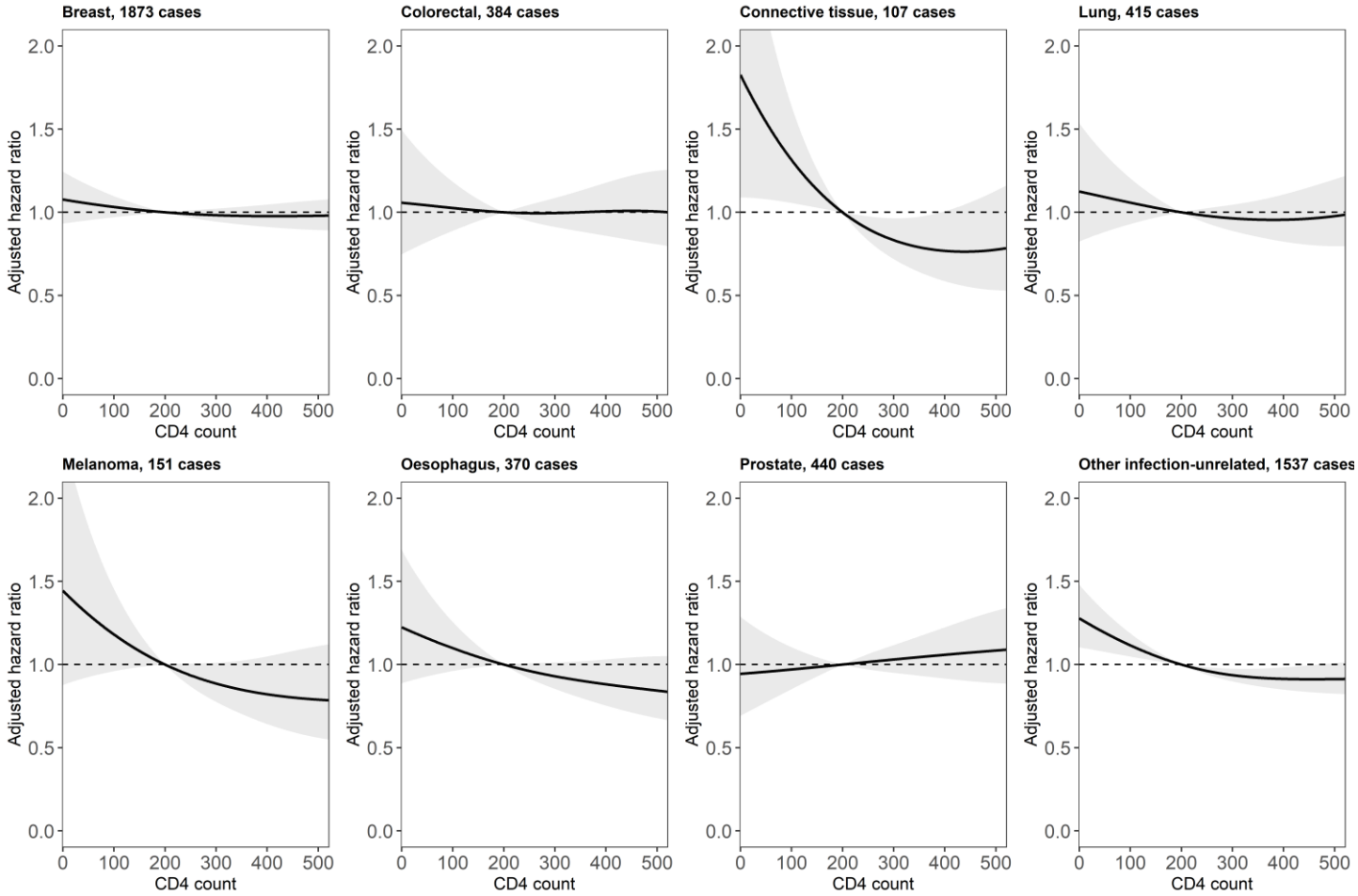

Figure 4