Published in final edited form as:

AIDS. 2013 June 1; 27(9): 1433–1441. doi:10.1097/QAD.0b013e32835f6b0c.

Predicting risk of cancer during HIV infection: the role of inflammatory and coagulation biomarkers

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Abstract

Objective—To investigate the relationship between inflammatory [interleukin-6 (IL-6) and C-reactive protein (CRP)] and coagulation (D-dimer) biomarkers and cancer risk during HIV infection.

Design—A prospective cohort.

Methods—HIV-infected patients on continuous antiretroviral therapy (ART) in the control arms of three randomized trials ($N = 5023$) were included in an analysis of predictors of cancer (any type, infection-related or infection-unrelated). Hazard ratios for IL-6, CRP and D-dimer levels ($\log_2$ -transformed) were calculated using Cox models stratified by trial and adjusted for demographics and CD4⁺ cell counts and adjusted also for all biomarkers simultaneously. To assess the possibility that biomarker levels were elevated at entry due to undiagnosed cancer,

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A.H.B., J.D.N. and J.D.L. contributed to the conception and design of the study. D.W. and J.D.N. performed all statistical analyses. A.H.B. drafted the manuscript. All authors contributed to data analysis and interpretation and reviewed the manuscript.

Conflicts of interest: There are no conflicts of interest.

analyses were repeated excluding early cancer events (i.e. diagnosed during first 2 years of follow-up).

Results—During approximately 24 000 person-years of follow-up (PYFU), 172 patients developed cancer (70 infection-related; 102 infection-unrelated). The risk of developing cancer was associated with higher levels (per doubling) of IL-6 (hazard ratio 1.38, $P < 0.001$), CRP (hazard ratio 1.16, $P = 0.001$) and D-dimer (hazard ratio 1.17, $P = 0.03$). However, only IL-6 (hazard ratio 1.29, $P = 0.003$) remained associated with cancer risk when all biomarkers were considered simultaneously. Results for infection-related and infection-unrelated cancers were similar to results for any cancer. Hazard ratios excluding 69 early cancer events were 1.31 ($P = 0.007$), 1.14 ($P = 0.02$) and 1.07 ($P = 0.49$) for IL-6, CRP and D-dimer, respectively.

Conclusion—Activated inflammation and coagulation pathways are associated with increased cancer risk during HIV infection. This association was stronger for IL-6 and persisted after excluding early cancer. Trials of interventions may be warranted to assess whether cancer risk can be reduced by lowering IL-6 levels in HIV-positive individuals.

Keywords

biomarkers; cancer; C-reactive protein; D-dimer; HIV; interleukin-6

Introduction

Since the beginning of the HIV pandemic, an increased risk of cancer has been observed in HIV-infected individuals. Some infection-related cancers, namely Kaposi sarcoma, non-Hodgkin lymphoma (NHL) and invasive cervical cancer (ICC), were found to have a particularly high incidence in patients with advanced HIV infection. With the aim of tracking the emerging epidemic, these cancers were included in the case definition of AIDS and, since then, have been classically referred to as AIDS-defining malignancies (ADMs) [1]. Epidemiological surveillance, however, subsequently broadened the spectrum of malignancies associated with HIV infection. HIV-infected individuals have been found to be at a higher risk of an ever-increasing range of both infection-related and infection-unrelated non-AIDS defining malignancies (NADMs) [2–5].

Although many reasons have been postulated, the mechanisms by which HIV infection increases the risk of cancer remain poorly understood. A higher prevalence of traditional cancer risk factors (e.g. smoking, alcohol use, oncogenic virus coinfection) in HIV-positive persons seems to play an important role [6]. Furthermore, clinical data suggest that HIV-associated immunodeficiency may lead to accelerated viral oncogenesis and reduced immune surveillance of malignant cells. Not only infection-related ADM but also infection-unrelated NADM have been shown to occur more frequently in HIV-infected persons, particularly in individuals with lower CD4⁺ cell counts [4,7–10]. Finally, the scale up of antiretroviral therapy (ART) has greatly improved survival outcomes, and as HIV-infected individuals age, the incidence of cancer is expected to increase [11], as it does in the general population.

Evidence has recently accrued suggesting that activated inflammatory and coagulation pathways may also contribute to cancer risk in HIV-infected individuals. In the Strategies for Management of Antiretroviral Therapy (SMART) study [12], structured interruptions of ART were associated with a significantly higher incidence of cancer [13] and a rise in plasma levels of D-dimer, a fibrin degradation product, and of interleukin-6 (IL-6), an inflammatory cytokine [14]. IL-6 production has been shown to be an important component of autocrine [15] and paracrine [16] circuits that fuel the growth of solid tumours. In the general population, elevated plasma levels of IL-6 and C-reactive protein (CRP), a marker of inflammation whose production by hepatocytes is driven by IL-6 [17], are associated with an increased risk of developing cancer [18–20]. Except for a few reports linking elevated IL-6 levels with the risk of future NHL [21,22], no systematic studies examining the interplay between inflammation, coagulation and cancer in the setting of HIV infection have been carried out.

The purpose of this study is to investigate the relationship between inflammatory (IL-6 and CRP) and coagulation (D-dimer) biomarkers and the risk of cancer during HIV infection. Our main *a priori* hypothesis was that activated inflammation and coagulation, as demonstrated by elevated plasma levels of IL-6, CRP and D-dimer, contribute to the risk of developing both infection-related and infection-unrelated cancer in HIV-infected individuals.

Materials and methods

Study design and study population

This is a cohort study involving participants in the control arms of three randomized controlled trials, who had consented to storing blood for future research and whose plasma levels of IL-6, CRP and D-dimer were measured at study entry ($N = 5023$). The methodology of SMART [12], the Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT) and the Subcutaneous Recombinant, Human Interleukin-2 in HIV-Infected Patients with Low CD4⁺ Counts under Active Antiretroviral Therapy (SILCAAT) [23] trial has been described in detail elsewhere. Briefly, the SMART trial compared, in 5472 individuals with CD4⁺ cell count more than 350 cells/ μ l at baseline, continuous use of ART versus structured treatment interruption guided by CD4⁺ cell count. The ESPRIT and SILCAAT trials compared IL-2 and ART with ART alone in 4111 individuals with CD4⁺ cell count more than 300 cells/ μ l and 1695 individuals with CD4⁺ cell count between 50 and 299 cells/ μ l, respectively. In the three trials, individuals in the control arms received standard of care according to HIV guidelines and were to be continuously maintained on ART.

Inflammatory and coagulation biomarkers

On the basis of strong associations of CRP, IL-6 and D-dimer with all-cause mortality in a nested case–control study [14] and the observation that these biomarkers were elevated in HIV-infected individuals compared with the general population [24], IL-6, CRP and D-dimer were measured on stored plasma at baseline for all consenting participants in ESPRIT, SILCAAT and SMART. For SMART participants, biomarkers were measured at the

Laboratory for Clinical Biochemistry Research at the University of Vermont (Burlington). In the ESPRIT and SILCAAT trials, laboratory measurements were performed by SAIC-Frederick (Frederick, Maryland, USA).

IL-6 was measured by the same method at each laboratory (Chemiluminescent Sandwich ELISA; R&D Systems, Minneapolis, Minnesota, USA). D-dimer levels were measured by ELISA on the Sta-R analyser, Liatest D-DI (Diagnostic Stago, Parsippany, New Jersey, USA) for SMART participants and on a VIDAS instrument (BioMerieux Inc., Durham, North Carolina, USA) for ESPRIT and SILCAAT participants. These assays, while different, compared very well on 20 duplicate samples. CRP was measured by ELISA by both laboratories. For SMART participants, an NBTMII nephelometer, N Antiserum to Human CRP (Siemens Diagnostics, Deerfield, Illinois, USA) was used. For ESPRIT and SILCAAT participants, an R&D Systems ELISA assay was used. The assays used were different, but as for D-dimer, they compared very well on duplicate samples. Lower limits of detection for IL-6, CRP and D-dimer were 0.16 pg/ml, 0.16 and 0.01 µg/ml for SMART. In ESPRIT and SILCAAT, lower limits of detection were 0.156 pg/ml, 0.078 and 0.045 µg/ml. All samples were analysed blinded to the treatment group and cancer event status.

Follow-up and cancer ascertainment

Patients were followed from study entry until first cancer event, death, loss to follow-up or the closing date of each study, whichever occurred first. Clinical assessment intervals and total follow-up time varied by study. Median follow-up time was 29 months in SMART, 81 months in ESPRIT and 91 months in SILCAAT; overall, median follow-up was 59 months for the entire cohort. In SMART and ESPRIT, all malignancies were systematically reported to and centrally adjudicated by the Endpoint Review Committee (ERC). In SILCAAT, only ADM and Hodgkin lymphoma were centrally adjudicated, whereas other NADMs were identified from the adverse event reporting system. In sensitivity analyses, the exclusion of SILCAAT had no major impact on findings (data not shown).

The following malignancies were considered to be infection-related: ADM, which have viral causes [Kaposi sarcoma, NHL and ICC are related to human herpes virus 8 (HHV-8), Epstein-Barr virus (EBV) and human papillomavirus (HPV), respectively]; vagina, vulva, penis, anal and oral cavity/pharynx cancers (HPV); Hodgkin lymphoma (EBV); liver cancer (hepatitis B and C viruses) and stomach cancer (*Helicobacter pylori*) [25]. No pharyngeal lymphoepitheliomas were identified in this study. All other malignancies were considered to be infection-unrelated cancers.

Statistical analyses

All analyses were restricted to patients in the control arms of each study for whom baseline biomarker data were available. Other than the events identified through adverse event reporting, cancer events were included if they were considered 'confirmed or 'probable' by the ERC, or if the patient died and the ERC attributed the underlying cause of death to cancer. Cancers were characterized by type on the basis of the Medical Dictionary for Regulatory Activities (MedDRA) High Level Term (HLT) assigned.

Kaplan–Meier curves giving the cumulative percentage of participants with cancer are shown for biomarker quartiles. To control for any differences in biomarker distributions among studies, quartiles were defined separately for participants in each study. Associations between IL-6, CRP and D-dimer levels at study entry and the risk of the first incident cancer event were estimated using proportional hazards (Cox) models from which hazard ratios corresponding to one $\log_2$ increase in biomarker (i.e. a doubling) and 95% confidence intervals (CIs) were estimated. Biomarkers were $\log_2$ -transformed because their distributions were right-skewed. Cox models for each biomarker were stratified by study to account for differences in underlying risk for the different cohorts. This stratification also served to stratify on the two laboratories that measured the biomarkers. Three models were considered: (1) unadjusted; (2) adjusting for age, sex, race, continent of enrolment, study entry and time-updated CD4⁺ counts; and (3) adjusting for the same covariates and all biomarkers simultaneously.

In order to compare the association of each biomarker with different types of cancer, a competing risk model for multiple unordered events of different types was fit [26]. With this approach, the fit of a model that assumed a common association for each biomarker with infection-related and infection-nonrelated cancers was compared with the fit of a model that allowed the association to vary. A similar approach was taken for assessing the association of the biomarkers with type-specific cancers of interest.

With the proportional hazards model, we assume that the risk of cancer associated with higher versus lower biomarker levels is constant over the follow-up period. This assumption was tested in a model that included an interaction term between each $\log_2$ -transformed biomarker and log follow-up time along with the baseline covariates in model (2) above. In addition, two other analyses were carried out: first, we produced graphic displays of log (–log) of the adjusted survival curves for participants with biomarker levels above versus below the median (departure from parallelism of these graphs indicates that the risk of cancer for those with higher versus lower levels is not constant over follow-up); and second, we performed analyses excluding cancer events diagnosed in the first 2 years of follow-up. These analyses were performed because clinically undetected malignancies may lead to raised plasma levels of inflammatory and coagulation biomarkers. In that case, one would expect that risk ratios for cancer events closer to the time of measurement of the biomarkers would differ from those events more remote from the measurement.

In other sensitivity analyses, additional important traditional cancer risk factors were adjusted for obesity/BMI (data available for participants in the three trials); diabetes (SMART and ESPRIT participants) and smoking (SMART only). All statistical analyses were performed using SAS software (version 9.2; SAS Institute, Cary, North Carolina, USA)

Results

A total of 5023 HIV-infected individuals were included. Six hundred and fifteen individuals without biomarker measurements were excluded. Excluded individuals were more likely to be younger, black and female and have lower nadir CD4⁺ cell counts (data not shown).

During approximately 24 000 persons-years of follow-up, 172 patients developed cancer (70 infection-related; 102 infection-unrelated). The most common infection-unrelated cancers were lung, prostate and colorectal; the most common infection-related cancers were NHL, anal and Hodgkin lymphoma (Table 1). Patients who developed cancer were more likely to be older males, have hepatitis B/C coinfection and diabetes, as well as to smoke. Patients who developed cancer were also found to have higher baseline levels of CRP, D-dimer and IL-6, and lower nadir CD4⁺ cell counts (Table 2).

Kaplan–Meier curves for any type, infection-related and infection-unrelated cancers are shown for quartiles of each biomarker in Supplementary Figure 1, <http://links.lww.com/QAD/A313>. When biomarkers were modelled as continuous variables, all three biomarkers demonstrated significant unadjusted associations (model 1) with increased risk of any type, infection-related and infection-unrelated cancers (see Table 3). After adjustment for demographics (age, race, sex and continent) and for study entry and time-updated CD4⁺ cell counts (model 2), each biomarker remained significantly associated with any type of cancer. When all biomarkers were adjusted for (model 3), only IL-6 remained independently associated with cancer risk (hazard ratio 1.29, 95% CI 1.09–1.52, $P = 0.003$). There was no evidence that biomarker associations varied between infection-related and infection-unrelated cancers. With the model 2 adjustment, P values for differences between the associations with infection-related and infection-unrelated cancers were 0.90, 0.90 and 0.89, for CRP, D-dimer and IL-6, respectively.

Table 4 summarizes the association between inflammatory and coagulation biomarkers and specific types of cancer that occurred in at least 10 patients. On the basis of the adjusted competing risk model summarizing cancers by type (NHL, Hodgkin lymphoma, HPV-related cancers, lung, prostate, colorectal, Kaposi sarcoma and all other types), there was no evidence that biomarker associations varied by type of cancer for D-dimer ($P = 0.12$) or IL-6 ($P = 0.65$); however, there was evidence for unequal effects across cancer types for CRP ($P = 0.04$). Higher baseline plasma levels of CRP were independently associated with risk of developing any type of lymphoma (hazard ratio 1.35, $P = 0.005$), Hodgkin lymphoma (HR = 1.72, $P = 0.004$) and colorectal cancer (hazard ratio 1.41, $P = 0.04$). Elevated IL-6, on the contrary, was found to be statistically associated with risk of lung cancer (hazard ratio 1.62, $P = 0.01$). However, owing to the limited number of cancer events and the consequent wider CI, our estimates are imprecise and need to be interpreted with caution.

Sensitivity analyses

For all cancers and for infection-related and infection-unrelated cancers, there was no evidence that hazard ratios for higher versus lower levels of CRP and D-dimer varied over follow-up; P values testing the proportionality assumption ranged between 0.25 and 0.92. For IL-6, however, the hazard ratios varied across time for all cancers ($P = 0.04$) and infection-unrelated cancers ($P = 0.03$). On the basis of model (2), the hazard ratio for any type of cancer in the first 2 years of follow-up (68 cancer events) associated with a doubling of IL-6 was 1.50 (95% CI 1.21–1.85; $P < 0.001$); for follow-up after 2 years (103 cancer events), the hazard ratio was 1.31 (95% CI 1.08–1.60; $P = 0.007$). For infection-unrelated cancers, the hazard ratios were 1.52 (95% CI 1.17–1.97, $P = 0.002$) and 1.24 (95% CI 0.95–

1.62, $P = 0.12$) for the two time periods. For IL-6, this is graphically illustrated in Supplementary Figure 2, <http://links.lww.com/QAD/A313>. During the early follow-up period, differences between the quartiles were greater, whereas after 1–2 years, the curves were more parallel.

Data on some important traditional cancer risk factors, namely obesity/BMI, diabetes and smoking, were not uniformly collected in the three trials. Consequently, these factors had to be adjusted for in smaller datasets (see Table 5). Their inclusion in multivariable models did not alter the associations between the biomarkers and risk of any type, infection-related and infection-unrelated cancer.

Discussion

This is the largest prospective study to investigate, in the setting of HIV infection, the relationship between plasma levels of coagulation and inflammatory biomarkers and cancer risk. Here, we report that activated inflammation and coagulation pathways, as measured by higher IL-6, CRP and D-dimer levels, are associated with an increased risk of cancer. This association was strongest for IL-6 and evident for both infection-related and infection-unrelated cancer after excluding early events and adjusting for demographics, CD4⁺ cell counts and traditional risk factors. During the entirety of follow-up, IL-6 had the steepest risk gradients for all cancer endpoints and, when the three biomarkers were entered into a multivariable Cox regression model, only IL-6 remained significantly associated with cancer risk.

The strong association between elevated plasma levels of IL-6 and cancer risk that we observed is corroborated by a body of evidence suggesting that IL-6 is a tumorigenic cytokine that influences, through autocrine [15] and paracrine [16] pathways, all stages of cancer development, including initiation, promotion, progression and dissemination [27]. Gene association studies using principles of Mendelian randomization have provided further evidence to support a role of IL-6 in cancer aetiology, with IL-6 gene polymorphisms associated with colorectal [28], cervical [29] and oral cancer [30].

In the present study, associations between CRP and cancer risk differed according to cancer type. Site-specific associations between inflammatory markers and cancer have also been described in the general population. Elevated plasma levels of CRP were found to be linked with lung [31,32] and colorectal cancer [31], but not with breast cancer [33]. On the contrary, a significantly increased risk of lung and colorectal cancer [18], but not of prostate cancer [34], was observed in HIV-uninfected individuals with raised circulating levels of IL-6. In contrast with the few previous reports in HIV-infected populations [21,22], we did not find a significant association between IL-6 and NHL. Instead, we did observe an association between CRP and Hodgkin lymphoma and all lymphomas grouped. Nevertheless, we had limited ability to examine site-specific associations, which should be confirmed in larger studies.

The possibility that raised plasma levels of biomarkers, rather than predicting clinical endpoints, just reflect the presence of subclinical disease (i.e. reverse causality) is difficult to

exclude in cancer or other diseases with long latency. In this study, risk gradients with CRP did not vary over follow-up and although risk gradients with IL-6 did vary over follow-up, hazard ratios associated with higher IL-6 levels remained significant for all cancers after exclusion of early cancer events. Furthermore, HIV-positive patients frequently have more aggressive cancer and poorer clinical outcomes [35]. Therefore, we consider it unlikely that our results can be explained by occult cancer.

The main strengths of our study are its large sample size, long follow-up period and carefully collected clinical data. A number of limitations need to be considered. First, the measurement of a more extensive panel of inflammatory and coagulation biomarkers would have been helpful to further clarify the relationship between activated inflammatory and coagulation pathways and the risk of cancer in HIV-infected individuals. Second, our analyses were not adjusted for some important traditional cancer risk factors, namely alcohol use, diet and sun exposure. Third, given the small numbers of cases, we were unable to carry out separate analyses for less common cancers and had no alternative but to use, as endpoints, broader cancer categories involving widely heterogeneous and etiologically distinct malignancies. However, this implies that the strong associations observed for IL-6 are conservative and may be stronger for individual cancers within broad categories. Finally, this study does not provide definitive evidence for a causal relationship between activated coagulation/inflammation and cancer during HIV infection; prospective gene association studies in HIV-infected individuals or a protective clinical effect on risk of cancer development from medical interventions able to specifically reduce the production or effect of IL-6 may be useful to elucidate this.

Our results indicate that activated inflammation and coagulation, as demonstrated by higher IL-6, CRP and D-dimer levels, are associated with the development of cancer during HIV infection. This association was strongest for IL-6 and was present for both infection-related and infection-unrelated malignancies after the exclusion of early events and after adjustment for demographics, CD4⁺ cell counts and traditional cancer risk factors. Trials of interventions may be warranted to assess whether cancer risk can be reduced by lowering IL-6 levels in HIV-positive individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to acknowledge the SMART, ESPRIT and SILCAAT participants and investigators (see *N Engl J Med* 2006; 355:2283–2296 for the complete list of SMART investigators and *N Engl J Med* 2009; 361:1548–1559 for the complete list of ESPRIT and SILCAAT investigators).

This study was funded by NIH [grant numbers: U01AI46957 and U01AI068641 (ESPRIT and SMART); U01AI042170 and U01AI46362 (SMART)].

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Table 1
Frequency distribution of cancers ESPRIT, SILCAAT and SMART control patients

	Number	Frequency (%)
Infection-unrelated cancers	102	100
Lung	26	26
Prostate	14	14
Colorectal	12	12
Breast	8	8
Melanoma	7	7
Urinary tract	6	6
Pancreas	3	3
Oesophagus	2	2
Leukemia	2	2
Unknown primary site	9	9
Other ^a	13	13
Infection-related cancers	70	100
Non-Hodgkin lymphoma	21	30
Anus	13	19
Hodgkin lymphoma	10	14
Kaposi sarcoma	10	14
Liver	5	7
Oral cavity/pharynx	4	6
Cervix	4	6
Other ^b	3	4

^aFemale reproductive tract, mesotheliomas, larynx, small intestine, thyroid, testicle, adrenal gland.

^bPenis, vagina, stomach.

Table 2
Baseline characteristics ESPRIT, SILCAAT and SMART control patients

	Developed cancer		<i>P</i> [*]
	Yes	No	
Age in years (median, IQR)	48 (41, 56)	42 (36, 49)	<0.001
Female sex (%)	12.2	22.7	0.005
Race (%)			0.05
Black	16.3	19.6	
White	76.7	67.2	
Other	7.0	13.1	
BMI (median, IQR)	24 (22, 26)	24 (22, 27)	0.67
AIDS (%)	25.0	26.1	0.67
Hepatitis B/C coinfection (%) ^a	27.9	18.6	0.04
Diabetes ^a	8.6	4.9	0.02
Smoking ^b	60.3	40.5	0.003
CD4 ⁺ cell count (cells/μl) (median, IQR)	421 (305, 585)	488 (370, 672)	0.27
CD4 ⁺ nadir (cells/μl)(median, IQR)	143 (44, 262)	200 (87, 319)	0.01
HIV RNA 500 copies/ml (%)	72.7	76.7	0.15
CRP (μg/ml) (median, IQR)	2.51 (1.25, 5.24)	1.54 (0.67, 3.54)	<0.001
D-dimer (μg/ml) (median, IQR)	0.28 (0.22, 0.47)	0.24 (0.15, 0.38)	<0.001
IL-6 (pg/ml) (median, IQR)	2.40 (1.80, 3.58)	1.80 (1.17, 2.80)	<0.001
Study			0.03
ESPRIT participant	40.7	35.2	
SILCAAT participant	25.6	13.6	
SMART participant	33.7	51.2	
No. of patients	172	4851	

CRP, C-reactive protein; IQR, interquartile range.

^a Not ascertained for patients in SILCAAT.

^b Not ascertained for patients in SILCAAT or ESPRIT.

^{*} *P* value from a univariate Cox regression model stratified by study.

Table 4
ESPRIT, SMART and SILCAAT hazard ratios for one log₂ (i.e. doubling) increment in biomarkers for cancer subsets

	CRP				D-dimer				IL-6			
	Adj HR ^a	95% CI	P		Adj HR ^a	95% CI	P		Adj HR ^a	95% CI	P	
Any cancer	1.16	1.06–1.26	0.001		1.17	1.01–1.35	0.03		1.38	1.19–1.59	<0.001	
No. of patients (events)		5022 (172)				5006 (171)				4994 (171)		
Lymphoma – any	1.35	1.09–1.66	0.005		1.31	0.93–1.85	0.12		1.34	0.95–1.88	0.10	
No. of patients (events)		5022 (31)				5006 (31)				4994 (31)		
Non-Hodgkin lymphoma	1.21	0.94–1.56	0.13		1.49	1.00–2.21	0.05		1.27	0.83–1.93	0.27	
No. of patients (events)		5022 (21)				5006 (21)				4994 (21)		
Hodgkin lymphoma	1.72	1.18–2.50	0.004		0.98	0.51–1.91	0.96		1.52	0.85–2.72	0.16	
No. of patients (events)		5022 (10)				5006 (10)				4994 (10)		
HPV-related cancers ^b	1.06	0.84–1.35	0.61		0.99	0.65–1.50	0.96		1.47	0.98–2.19	0.06	
No. of patients (events)		5022 (23)				5006 (23)				4994 (23)		
Lung cancer	1.26	1.00–1.58	0.05		0.84	0.58–1.20	0.34		1.62	1.12–2.35	0.01	
No. of patients (events)		5022 (26)				5006 (25)				4994 (25)		
Prostate cancer	0.84	0.62–1.15	0.28		0.91	0.59–1.42	0.68		0.62	0.33–1.17	0.14	
No. of patients (events)		5022 (14)				5006 (14)				4994 (14)		
Colorectal cancer	1.41	1.02–1.94	0.04		0.95	0.56–1.59	0.84		1.32	0.77–2.26	0.31	
No. of patients (events)		5022 (12)				5006 (12)				4994 (12)		
Kaposi sarcoma	1.05	0.72–1.51	0.81		1.55	0.93–2.57	0.09		1.58	0.92–2.69	0.09	
No. of patients (events)		5022 (10)				5006 (10)				4994 (10)		

CI, confidence interval; CRP, C-reactive protein; HPV, human papillomavirus.

^aHR, hazard ratio for one log₂ increase in indicated biomarker. Model is stratified by study and adjusted for demographics (age, race, sex and continent), and study entry and time-updated CD4⁺ cell counts.

^bInvasive cervical cancer, anal, vagina, vulva, penis and oral cavity/pharynx.

Table 5

Sensitivity analysis – adjustment for BMI, diabetes and smoking hazard ratios for one log₂ (i.e. doubling) increment in biomarkers ESPRIT, SMART and SILCAAT

	CRP		D-dimer		IL-6	
	HR ^b	P	HR ^b	P	HR ^b	P
Any cancer						
Full adjustment ^a	1.16	0.001	1.17	0.03	1.38	<0.001
No. of patients (events)	5022 (172)		5006 (171)		4994 (171)	
Full adjustment + BMI	1.16	<0.001	1.16	0.04	1.37	<0.001
No. of patients (events)	4948 (170)		4932 (169)		4920 (169)	
Full adjustment + smoking (SMART)	1.10	0.20	1.12	0.28	1.37	0.006
No. of patients (events)	2541 (58)		2526 (57)		2514 (57)	
Full adjustment + diabetes (SMART and ESPRIT)	1.15	0.008	1.14	0.10	1.42	<0.001
No. of patients (events)	4307 (128)		4291 (127)		4279 (127)	
Infection-related cancer						
Full adjustment ^a	1.18	0.02	1.19	0.13	1.42	0.002
No. of patients (events)	5022 (70)		5006 (70)		4994 (70)	
Full adjustment + BMI	1.18	0.02	1.19	0.15	1.40	0.004
No. of patients (events)	4948 (69)		4932 (69)		4920 (69)	
Full adjustment + smoking (SMART)	1.15	0.30	1.25	0.22	1.45	0.07
No. of patients (events)	2541 (18)		2526 (18)		2514 (18)	
Full adjustment + diabetes (SMART & ESPRIT)	1.20	0.03	1.25	0.08	1.56	<0.001
No. of patients (events)	4307 (51)		4291 (51)		4279 (51)	
Infection-unrelated cancer						
Full adjustment ^a	1.15	0.02	1.15	0.12	1.35	0.002
No. of patients (events)	5022 (102)		5006 (101)		4994 (101)	
Full adjustment + BMI	1.15	0.02	1.15	0.13	1.35	0.002
No. of patients (events)	4948 (101)		4932 (100)		4920 (100)	
Full adjustment + smoking (SMART)	10.08	0.39	1.06	0.65	1.35	0.04
No. of patients (events)	2541 (40)		2526 (39)		2514 (39)	

	CRP		D-dimer		IL-6	
	HR ^b	P	HR ^b	P	HR ^b	P
Full adjustment + diabetes (SMART & ESPRIT)	1.12	0.10	1.08	0.45	1.32	0.02
No. of patients (events)	4307 (77)		4291 (76)		4279 (76)	

CRP, C-reactive protein.

^aStratified by study and adjusted for demographics (age, race, sex, continent), and study entry and time-updated CD4⁺ cell counts.

^bHR, hazard ratio for one log2 increase in indicated biomarker.