Immune-activation markers and subsequent cancer onset in people with HIV: A Case-Control study

By the INSIGHT Cancer Working Group

For the ESPIRIT, FIRST, INSIGHT SMART and START Study Groups

Poster J-03/633

BACKGROUND

- People with HIV (PWH) experience persistently increased risk of cancer, specifically infection-related cancer, and cancer-related mortality as compared with the general population in the modern era of antiretroviral therapy (ART).
- The excess is pronounced in infection-related cancers, which includes non-Hodgkin lymphoma, and reflects the combined effects of chronic immune activation, impaired immune surveillance and oncogenic viral coinfections.
- B-cell dysregulation is central to the pathogenesis of several cancers in PWH, particularly lymphomas, which arise for several reasons including prolonged antigenic stimulation.
- Identifying immune-related biomarkers that precede a cancer diagnosis may inform risk stratification and surveillance strategies among PWH.
- Prospective cohort studies have demonstrated that B-cell activation markers, which are indicative of B-cell dysregulation, are associated with onset of HIV-associated lymphomas. However, many of these prior studies were conducted in early ART eras.

We conducted a nested case-control study to evaluate whether baseline B-cell activation markers (sCD23, sCD27, sCD30 and CXCL13) are associated with subsequent cancer risk.

METHODS

- Data from participants in four clinical trials (ESPIRIT, FIRST, SMART and START) led by the INSIGHT group evaluating ART strategies were used.
- Incident cancer cases included: infection-related cancers were defined as those caused by infectious agents including lymphoma diagnoses. All other malignancies were infection-unrelated cancers.
- Cases were individually matched on a 1 to 2 basis with controls who did not experience an AIDS event, serious non-AIDS event or death. Matching criteria included: study, ART group, age and randomization date.
- Four biomarkers were measured using an ELISA per manufacturer's instructions on plasma that was stored at baseline from all cases and controls.
- Conditional logistic regression analyses for matched case-control studies were evaluated the association of each biomarker and cancer risk (for all cancers, infection-unrelated, related cancers and lymphomas).
- Separate analyses by biomarker tertile of each biomarker (defined using cases and controls combined) were performed and ORs for each of the two upper tertiles versus the lowest tertile (reference group) are noted along with 95% confidence intervals (CIs) and p-values.
- Spearman correlation coefficients were used to assess the association between B-cell activation biomarkers with baseline CD4 T-cell and HIV viral load in cancer cases.

B-cell activation biomarkers CXCL13 and sCD30 were associated with subsequent risk of infection-related cancers among people with HIV.

RESULTS

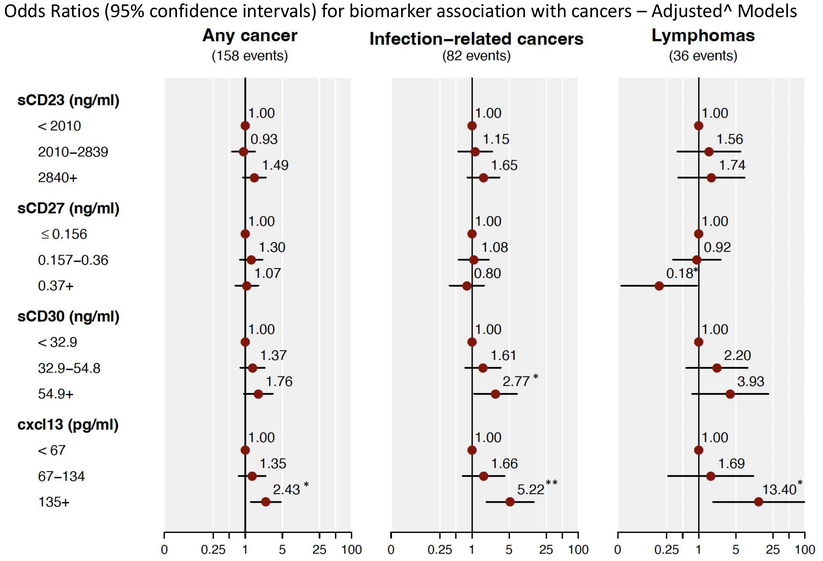
- A total of 158 participants who developed incident cancer during follow-up were identified from the INSIGHT trials and matched to 313 controls.
- There were 82 cases of infection-related cancers, 79 cases infection-unrelated cancers and 36 lymphoma cases.
- The median time from study entry to cancer diagnosis among cases was 2.9 years. At the time of cancer diagnosis, the median CD4 T-cell count was 525 cells/mm³, the median HIV RNA level was 125 copies/mL, and 79% of participants were receiving antiretroviral therapy.

Table 1: Baseline B-cell activation markers in participant cases and controls

	Cases (N=158) Median (IQR)	Controls (N=313) Median (IQR)
sCD23 pg/ml	2574.5 (1811.0, 3528.2)	2390.8 (1825.2, 3083.6)
sCD27** ng/ml	0.25 (0.16, 0.43)	0.24 (0.16, 0.50)
sCD30 ng/ml	44.1 (31.6, 68.8)	42.0 (28.4, 58.3)
CXCL13 pg/ml	113.3 (63.9, 176.3)	90.8 (49.8, 146.5)

** 49 (31%) of cases and 109 (35%) of controls had below the lower limit of detection (0.156 ng/ml)

Figure 1: Odds Ratios (95% confidence intervals) for biomarker association with cancers – Adjusted^ Models



^Adjusted for age, gender, baseline CD4, and baseline $\log_{10}$ HIV-RNA and taking matching into account
*P-value ≤0.05 **P-value ≤0.005

RESULTS

- Participants in the highest tertiles of sCD30 and CXCL13 had approximately 2.77 and 5.22 increased odds, respectively, of developing infection-related cancers compared with those in the lowest tertiles after adjustment.
- Among the 36 participants who developed lymphoma, CXCL13 was the only biomarker that was significantly positively associated with subsequent lymphoma risk (**Figure 1**).
- There were no associations between baseline B-cell activation biomarkers and infection-unrelated cancers.
- No associations were observed between lymphoma and sCD23, sCD27 or sCD30. An inverse association observed for sCD27 in the highest tertile, likely driven by the small sample size rather than a protective effect.
- There was a positive and significant correlation between sCD30 and sCD23 and CXCL13. HIV RNA levels at baseline was also positively correlated with sCD30 and CXCL13 (**Table 2**).

	Spearman Correlation Coefficients – Cancer Cases Prob > |r| under H0: Rho=0 Number of Observations					
	SCD23	**SCD27**	**SCD30**	**CXCL13**	**cd4bl**	**rnabl**
SCD23 pg/ml	1.00000	-0.01831 0.8194	0.33320 **<.0001**	0.11316 0.1569	-0.04986 0.5339	0.02422 0.7626
SCD27 ng/ml	-0.01831 0.8194	1.00000	-0.11397 0.1539	-0.05074 0.5267	0.01453 0.8562	-0.00929 0.9078
SCD30 ng/ml	0.33320 **<.0001**	-0.11397 0.1539	1.00000	0.64367 **<.0001**	0.01776 0.8247	0.52976 **<.0001**
CXCL13 pg/ml	0.11316 0.1569	-0.05074 0.5267	0.64367 **<.0001**	1.00000	0.14352 0.0720	0.59838 **<.0001**
cd4bl CD4 baseline	-0.04986 0.5339	0.01453 0.8562	0.01776 0.8247	0.14352 0.0720	1.00000	0.19425 0.0145
rnabl RNA baseline	0.02422 0.7626	-0.00929 0.9078	0.52976 **<.0001**	0.59838 **<.0001**	0.19425 0.0145	1.00000

Table 2: Spearman correlation to evaluate association between B-cell activation biomarkers, CD4 T-cell and HIV viral load at baseline among cancer cases.

CONCLUSIONS

B-cell activation biomarkers CXCL13 and sCD30 were associated with subsequent risk of infection-related cancers among people with HIV. CXCL13 was also associated with lymphoma risk in this cohort.

ACKNOWLEDGMENTS

The authors wish to thank the trial participants and their families as well as the many collaborators on this study.

Funding was provided by the following NIH grants: UM1-AI068641, UM1-AI120197, U01-AI136780, U01-AI46957, U01-AI046362, and U01-AI042170.

Supported by the National Institute of Allergy and Infectious Diseases, National Institutes of Health Clinical Center, National Cancer Institute, National Heart, Lung, and Blood Institute, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institute of Mental Health, National Institute of Neurological Disorders and Stroke, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (France), National Health and Medical Research Council (Australia), National Research Foundation (Denmark), Bundes ministerium für Bildung und Forschung (Germany), European AIDS Treatment Network, Medical Research Council, National Institute for Health Research, National Health Service (United Kingdom), and University of Minnesota. Antiretroviral drugs were donated to the central drug repository by AbbVie, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline/ViiV Healthcare, Janssen Scientific Affairs, and Merck.

Presenter Contact Information:

Email:ramya.ramaswami@nih.gov