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Biomarker Dynamics in B-cell Lymphoma: A Longitudinal Prospective Study of Plasma Samples Up to 25 Years before Diagnosis

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Abstract

The B-cell activation markers CXCL13, sCD23, sCD27, and sCD30 are associated with future lymphoma risk. However, a lack of information about the individual dynamics of marker–disease association hampers interpretation. In this study, we identified 170 individuals who had donated two prediagnostic blood samples before B-cell lymphoma diagnosis, along with 170 matched cancer-free controls from the Northern Sweden Health and Disease Study. Lymphoma risk associations were investigated by subtype and marker levels measured at baseline, at the time of the repeated sample, and with the rate of change in the marker level. Notably, we observed strong associations between CXCL13, sCD23, sCD27, and sCD30 and lymphoma risk in blood samples collected 15 to 25 years before diagnosis. B-cell activation marker levels increased among future lymphoma cases over time, while remaining stable among controls. Associations between slope and risk were strongest for indolent lymphoma subtypes. We noted a marked association of sCD23 with chronic lymphocytic leukemia ($OR_{slope} = 28$, $P_{trend} = 7.279 \times 10^{-10}$). Among aggressive lymphomas, the association between diffuse large B-cell lymphoma risk and slope was restricted to CXCL13. B-cell activation seemed to play a role in B-cell lymphoma development at early stages across different subtypes. Furthermore, B-cell activation presented differential trajectories in future lymphoma patients, mainly driven by indolent subtypes. Our results suggest a utility of these markers in predicting the presence of early occult disease and/or the screening and monitoring of indolent lymphoma in individual patients. *Cancer Res; 77(6); 1408–15. ©2017 AACR.*

Introduction

Immunodeficiency and autoimmunity are strong B-cell lymphoma risk factors (1). B-cell lymphoma development has been linked to aberrant B-cell activation in response to several infections (2, 3). Further evidence that sustained B-cell activation plays a role in B-cell lymphoma development is provided by eight prospective studies showing associations between elevated blood concentrations of B-cell activation markers, including soluble (s) CD23, sCD27, sCD30, and CXCL13 and subsequent B-cell lymphoma risk among the general population (4–11). Other immune markers, such as sTNF-R1, have been less consistently associated with B-cell lymphoma risk (12). sTNF-R1, sCD27, and sCD30 are soluble forms of receptors of the TNF receptor superfamily. While sTNF-R1 mediates TNFα effects (13), both sCD27 and sCD30 have a crucial role in regulating cellular activity in subsets of T-, B-, and natural killer cells (14, 15). The soluble form of CD23, which is a Fc receptor for IgE, is released from activated B cells and is itself a stimulator of B-cell proliferation, inducing antibody class switching (16). CXCL13, the ligand of CXCR5, is a homeostatic chemokine that partly regulates B-cell trafficking (17).

All previous studies investigating circulating B-cell activation markers and B-cell lymphoma risk among the general population (4–11) have been based on single biological samples per participant, collected on average about 7 years before diagnosis. Therefore, some of the signals reported by these studies might be influenced due to early stages of disease (i.e., reverse causation). Moreover, and more important, these studies preclude to study the individual dynamics of the marker–disease association. To better understand the natural history of these markers, their role in lymphomagenesis and their clinical applicability, we examined concentrations of CXCL13, sTNF-R1, sCD23, sCD27, and sCD30 in repeated plasma samples up to 25 years before diagnosis from future B-cell lymphoma patients and matched controls. The dynamics of immune markers were modeled on an individual level in relation to B-cell lymphoma risk; Given that lymphomagenesis is likely to be a dynamic process, we hypothesized that these markers may display differential dynamic trajectories in future B-cell lymphoma patients.

Materials and Methods

Study population

We performed a nested case–control study within the Northern Sweden Health and Disease Study (NSHDS; ref. 18), which was

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approved by the local research ethics committee at Umeå University (Umeå, Sweden). The NSHDS includes 138,900 participants who donated more than 210,000 blood samples (by March 2015). Repeated samples from same individuals typically have been donated with a 10-year interval. Study recruitment began in 1985. After attaining informed consent, survey data using a standardized questionnaire and a blood sample were collected. Samples were collected in EDTA plasma vacutainers that were frozen within 1 hour and stored at −80°C at the Medical Biobank at Umeå University Hospital (Umeå, Sweden). We identified 170 individuals with B-cell lymphoma who had donated two prediagnostic blood samples to the NSHDS by linkage with the Swedish Cancer Registry. B-cell lymphoma cases were diagnosed 13.2 ± 4.4 and 5.5 ± 4.0 years (mean ± SD) after donation of the prediagnostic baseline, and repeated sample, respectively. Cases were classified according to SEER ICD-O-3 codes (19). Diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, and Mantle cell lymphoma were considered aggressive lymphoma subtypes, while follicular lymphoma (grades 1, 2, and 3a), chronic lymphocytic leukemia (CLL), MALT lymphoma, lymphoplasmacytic lymphoma, and hairy cell leukemia were considered indolent subtypes (Table 1). Controls were matched to cases on a 1:1 ratio on sex, age (±5 months), and blood draw dates (±2 months) from subjects who had two blood samples available and were alive and free of cancer at time of diagnosis of the matched case. From two included case–control pairs, one of the prediagnostic samples had insufficient volume for analyses. Cases and controls were balanced concerning fasting status before blood sample collection and most samples had not been thawed before ($N = 654$). One-third of the cases ($N = 60$), using a single biological sample, were included in a previous study (9).

Plasma CXCL13, sTNF-R1, sCD23, sCD27, and sCD30

Biomarker levels were measured by ELISA assays (eBioscience) to measure sCD23, sCD27, and sCD30 and by a Luminex bead-based multiplex assay (R&D Systems) to measure CXCL13 and sTNF-R1. Assays were performed according to the manufacturers' protocols. Matched case–control pairs and repeated samples were placed proximal to each other but in random order on the same assay plate. Laboratory personnel were blinded for case–control status. The available plasma volume allowed us to measure all markers, besides sCD30, in duplicate. Quality control samples were included on every plate. Inter- and intra-assay coefficients of variation were 41.9% and 10.7% for CXCL13, 15.3% and 7.2% for sTNF-R1, 19.2% and 10.9% for sCD23, 45.7% and 12.5% for sCD27, and 15.4% for sCD30 (not measured in duplicate), respectively.

Statistical analysis

Immune marker concentrations were log10 transformed to normalize their distributions. Missing values, as concentrations were below or above the limit of quantification (i.e., 0.6% of all measures), were imputed. The multiple imputation model included log-transformed marker concentrations, case–control status, and analysis plate. To reduce the influence of extreme concentrations, concentration data were winsorized to the 1st and 99th percentile. Body mass index (BMI) and smoking status were included as covariates in all statistical models. If BMI ($N = 45$) or smoking status ($N = 5$) was missing at one time-point of blood draw, the corresponding value from the other sampling time point from the same individual was used.

Table 1. Characteristics of the blood samples and the study population

	Cases *N* (%) 170	Controls *N* (%) 170	P[a]
Age at sample collection, years			
Baseline sample, mean (range)	52 (30–69)	52 (30–69)	
Repeated sample, mean (range)	59.7 (40–74)	59.7 (40–73)	
Sex			
Female	111 (65.3)	111 (65.3)	
Male	59 (34.7)	59 (34.7)	
Body mass index			
Baseline sample, mean (SD)	25.9 (3.9)	25.3 (3.5)	0.10
Repeated sample, mean (SD)	26.8 (4.2)	26.1 (4.2)	0.13
Smoking status			
Baseline sample			0.36
Nonsmoker	96 (56.5)	94 (55.3)	
Current smoker	31 (18.2)	41 (24.1)	
Former smoker	42 (24.7)	35 (20.6)	
Repeated sample			0.20
Nonsmoker	108 (63.5)	106 (62.4)	
Current smoker	20 (11.8)	31 (18.2)	
Former smoker	41 (24.1)	33 (19.4)	
Individual fasting status			
Baseline sample			0.99
0–4 hours	44 (26.0)	45 (26.6)	
4–8 hours	27 (16.0)	26 (15.4)	
>8 hours	98 (58.0)	98 (58.0)	
Repeated sample			0.92
0–4 hours	72 (42.6)	74 (43.5)	
4–8 hours	4 (2.4)	5 (2.9)	
>8 hours	93 (55.0)	91 (53.5)	
Thawing cycles before			
Baseline sample			0.48
No	158 (93.5)	161 (95.3)	
Once	11 (6.5)	8 (4.7)	
Repeated sample			1.00
No	167 (98.2)	168 (98.8)	
Once	3 (1.8)	2 (1.2)	
B-cell lymphoma subtypes			
Diffuse large B-cell lymphoma[b]	43 (25.3)		
Follicular lymphoma[c]	30 (17.6)		
Chronic lymphocytic leukemia[c]	51 (30.0)		
MALT lymphoma[c]	4 (2.4)		
Burkitt lymphoma[b]	2 (1.2)		
Lymphoplasmacytic lymphoma[c]	16 (9.4)		
Mantle cell lymphoma[b]	4 (2.4)		
Hairy cell leukemia[c]	7 (4.1)		
B-cell lymphoma unspecified	12 (7.1)		
Hairy cell leukemia variant[c]	1 (0.6)		

[a]*P* values calculated using paired *t* test for continuous and χ^2 test for categorical variables.
[b]Considered aggressive B-cell lymphoma subtypes.
[c]Considered indolent B-cell lymphoma subtypes.

We sought to investigate differences of immune marker trajectories between future cases and controls, fitting a linear mixed effects model using restricted maximum likelihood. For a given protein (Y), the model for the j:th measurement (i.e., baseline, or repeated measure) from individual i can be described as:

$$Y_{ij} = \beta_0 + \beta_1 CaCo_i + \beta_2 CaCo_i{}^* time_{ij} + \beta_3 SmS_{ij} + \beta_4 BMI_{ij} + (1|i) + (1|CaCo\text{-}pair_i) + \varepsilon_{ij}$$

β_0 is the intercept, $CaCo_i$ indicates the case–control status for individual i, and ε_{ij} is the residual error. $CaCo_i{}^* time_{ij}$ is the interaction term between case–control status and time, where time was set to zero at the date of case diagnosis. BMI (BMI_{ij}) and smoking status (SmS_{ij}) were included as fixed effects. Intercepts for

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Table 2. OR and 95% confidence interval for marker measures and B-cell lymphoma risk for prediagnostic baseline and repeated sample and cases with 15–25 years and 0–3 years between blood draw and diagnosis

	Baseline[b]	B-cell lymphoma		15–25 years		Repeated[b]	B-cell lymphoma		0–3 years	
Analyte[a]	$N_{Controls}$	*N*	OR[c] (95% CI)	*N*	OR[d] (95% CI)	$N_{Controls}$	*N*	OR[c] (95% CI)	*N*	OR[d] (95% CI)
CXCL13 (pg/mL)										
≤50.02	42	31	Ref	6	Ref	42	28	Ref	5	Ref
50.03–67.82	42	37	1.33 (0.67–2.67)	17	3.71 (1.22–11.30)	46	22	0.61 (0.28–1.31)	4	0.79 (0.19–3.36)
67.83–86.79	42	25	0.83 (0.38–1.83)	10	1.53 (0.48–4.88)	31	29	1.67 (0.77–3.60)	7	2.74 (0.72–10.35)
≥86.80	42	75	4.37 (1.94–9.83)	26	5.44 (1.89–15.73)	51	91	3.52 (1.77–6.97)	39	11.98 (3.69–38.94)
P_{trend}[e]			1.810×10^{-4}		0.006			7.578×10^{-6}		6.737×10^{-8}
sTNF-R1 (pg/mL)										
≤2,953	42	40	Ref	11	Ref	33	24	Ref	7	Ref
2,954–3,436	42	35	0.92 (0.49–1.73)	13	1.46 (0.55–3.91)	34	34	1.70 (0.73–3.91)	8	1.41 (0.43–4.59)
3,437–4,007	42	37	1.00 (0.53–1.86)	13	1.34 (0.50–3.58)	47	37	1.36 (0.62–3.00)	9	1.03 (0.33–3.20)
≥4,008	42	56	1.63 (0.79–3.40)	22	2.32 (0.91–5.91)	56	75	2.57 (1.13–5.82)	31	2.92 (1.08–7.91)
P_{trend}			0.199		0.088			0.030		0.010
sCD23 (pg/mL)										
≤1,525	42	16	Ref	4	Ref	40	15	Ref	5	Ref
1,526–2,133	43	29	2.34 (1.01–5.45)	14	4.76 (1.21–18.80)	32	25	3.10 (1.26–7.63)	6	1.87 (0.50–7.07)
2,134–2,768	42	36	2.55 (1.08–6.04)	13	4.70 (1.16–19.01)	43	20	1.31 (0.54–3.18)	3	0.67 (0.15–3.08)
≥2,769	42	87	6.21 (2.77–13.92)	28	10.29 (2.65–39.98)	55	110	7.38 (3.19–17.03)	41	10.59 (3.42–32.80)
P_{trend}			1.507×10^{-6}		4.713×10^{-4}			2.565×10^{-7}		2.262×10^{-7}
sCD27 (U/mL)										
≤11.87	42	20	Ref	8	Ref	37	17	Ref	6	Ref
11.88–17.14	42	38	3.15 (1.31–7.59)	13	1.44 (0.50–4.12)	40	30	1.98 (0.86–4.57)	8	1.23 (0.37–4.08)
17.15–23.71	42	56	5.52 (2.15–14.18)	18	2.39 (0.89–6.41)	54	42	2.49 (1.11–5.61)	7	0.81 (0.24–2.69)
≥23.72	42	54	6.64 (2.35–18.72)	20	2.66 (1.00–7.09)	39	81	7.25 (3.03–7.39)	34	5.35 (1.96–14.56)
P_{trend}			0.002		0.034			1.489×10^{-6}		1.129×10^{-5}
sCD30 (ng/mL)										
≤1.97	42	33	Ref	9	Ref	46	29	Ref	5	Ref
1.98–2.39	42	28	0.94 (0.49–1.82)	6	0.74 (0.23–2.37)	42	24	0.89 (0.43–1.82)	5	1.11 (0.30–4.18)
2.40–3.11	42	45	1.35 (0.69–2.65)	17	1.76 (0.66–4.71)	32	32	1.37 (0.70–2.67)	9	2.93 (0.86–9.99)
≥3.12	42	62	2.29 (1.15–4.59)	27	3.96 (1.55–10.12)	50	85	3.15 (1.66–5.99)	36	8.02 (2.79–23.09)
P_{trend}			0.006		2.510×10^{-4}			5.638×10^{-5}		7.599×10^{-7}

Abbreviation: CI, confidence interval.

[a]Analyte concentrations categorized into quartiles based on the distribution among controls in prediagnostic sample 1 (baseline).

[b]Time to diagnosis for the baseline sample is 13.2 ± 4.4 years and for the repeated sample 5.5 ± 4.0 years (mean ± SD).

[c]ORs calculated by conditional logistic regression adjusted for body mass index and smoking status.

[d]ORs calculated by nonconditional logistic regression adjusted for sex, age, blood draw date, analysis plate, body mass index, and smoking status.

[e]Two-sided *P* values were calculated by including median values of analyte quartiles as continuous variable.

individuals $(1|i)$ and for matched case–control pairs $(1|CaCo\text{-}pair_i)$ were included as random effects. Satterthwaite approximation was used to estimate degrees-of-freedom and *P* values. The linear mixed model was fitted using the lme4 package in the R environment for statistical computing (The R Foundation for Statistical Computing).

Baseline and repeated samples were also analyzed separately. Marker levels were categorized into quartiles (Q), using Q values from controls at baseline as cutoffs. The whole study population and specific subsets of interest were analyzed (Table 2). Further analyses on Q categorized data were performed to investigate whether increase in immune marker concentration over time, or concentration measured at baseline was stronger associated with risk (Table 5). Conditional logistic regression was applied, analyzing the whole study group. Subset analyses were done using nonconditional logistic regression to maintain statistical power, adjusting for matching factors and analysis plate. Baseline and slope measures were weakly correlated in all markers with Spearman correlation coefficients between 0.12 (sTNF-R1), and 0.21 (sCD30). Tests for trend were calculated using the quartile medians as a continuous variable.

Potential confounding due to fasting status was evaluated as it had a small effect on sCD30. Risk estimates changed below one percent when it was included as a covariate, thus it was not included in the final regression model. Performing sensitivity analyses by excluding previously thawed samples, it was noted that risk estimates were hardly affected, all significances remained, and it had no bearing on the interpretation of results; therefore, we present the results including these samples. Multiple imputation and logistic regression analyses were performed using SPSS, version 23 (IBM). All *P* values are two-sided, with $P < 0.05$ considered as statistically significant.

Results

Trajectories of B-cell activation markers were investigated in 170 future B-cell lymphoma patients, and 170 matched cancer-free controls. Median age at lymphoma diagnosis was 65.2 ± 8.1 years (±SD). Characteristics of the study population are shown in Table 1. Investigating controls separately, we found a correlation between older age and plasma concentrations of CXCL13 ($P = 0.036$) and sTNF-R1 ($P = 1.560 \times 10^{-5}$). Men had higher levels of CXCL13 ($P = 0.048$) and sTNF-R1 ($P = 0.002$), while sCD30 was higher in females ($P = 0.030$). BMI was positively correlated with sTNF-R1 ($P = 4.0 \times 10^{-5}$) and sCD23 ($P = 0.015$). Current smokers had lower concentrations of sCD23 ($P = 0.003$) and sCD30 ($P = 0.035$) compared with nonsmokers. All marker concentrations were weakly to moderately correlated with Spearman correlation coefficients between 0.04 (CXCL13 and sCD27) and 0.32 (sCD23 and sCD30).

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Table 3. Results from linear mixed effects modeling

	B-cell lymphoma ($N = 170$)			CLL ($N = 51$)			Follicular lymphoma ($N = 30$)			DLBCL ($N = 42$)		
Parameter[a]	β	SE	*P*	β	SE	*P*	β	SE	*P*	β	SE	*P*
CXCL13												
Intercept	1.833	0.079	$<1.0 \times 10^{-15}$	1.633	0.213	2.6×10^{-13}	1.634	0.232	1.9×10^{-11}	1.670	0.225	1.5×10^{-12}
Control-case[b]	0.263	0.036	1.8×10^{-12}	0.123	0.041	0.003	0.336	0.051	1.5×10^{-10}	0.277	0.046	3.8×10^{-9}
Controls × time[c]	−0.002	0.002	0.430	−0.002	0.003	0.511	−0.003	0.003	0.355	−0.002	0.003	0.490
Cases × time[d]	0.012	0.002	3.7×10^{-8}	0.004	0.004	0.283	0.016	0.004	1.6×10^{-4}	0.014	0.004	5.4×10^{-4}
sTNF-R1												
Intercept	3.416	0.036	$<1.0 \times 10^{-15}$	3.077	0.104	$<1.0 \times 10^{-15}$	3.086	0.116	$<1.0 \times 10^{-15}$	3.133	0.108	$<1.0 \times 10^{-15}$
Control-case	0.034	0.016	0.030	0.055	0.020	0.006	0.007	0.025	0.795	−0.017	0.022	0.433
Controls × time	0.003	0.001	0.003	−0.001	0.001	0.379	−0.001	0.001	0.483	−0.001	0.001	0.651
Cases × time	0.004	0.001	8.4×10^{-7}	0.002	0.002	0.239	0.000	0.002	0.967	−0.002	0.002	0.338
sCD23												
Intercept	3.196	0.075	$<1.0 \times 10^{-15}$	3.010	0.202	$<1.0 \times 10^{-15}$	3.145	0.215	$<1.0 \times 10^{-15}$	3.126	0.198	$<1.0 \times 10^{-15}$
Control-case	0.320	0.032	$<1.0 \times 10^{-15}$	0.629	0.038	$<1.0 \times 10^{-15}$	0.348	0.045	1.0×10^{-13}	0.135	0.039	5.9×10^{-4}
Controls × time	0.001	0.002	0.410	−0.003	0.003	0.258	0.000	0.003	0.868	0.000	0.002	0.959
Cases × time	0.015	0.002	$<1.0 \times 10^{-15}$	0.025	0.003	5.5×10^{-13}	0.015	0.004	4.3×10^{-5}	0.004	0.003	0.241
sCD27												
Intercept	1.287	0.097	$<1.0 \times 10^{-15}$	0.897	0.213	3.2×10^{-5}	0.981	0.213	6.4×10^{-6}	1.005	0.210	2.8×10^{-6}
Control-case	0.238	0.041	1.2×10^{-8}	0.358	0.041	$<1.0 \times 10^{-15}$	0.169	0.049	0.001	0.150	0.044	6.7×10^{-4}
Controls × time	0.002	0.002	0.320	−0.001	0.003	0.770	−0.001	0.003	0.604	−0.001	0.003	0.698
Cases × time	0.014	0.002	2.4×10^{-12}	0.020	0.004	2.7×10^{-7}	0.009	0.004	0.029	0.007	0.004	0.070
sCD30												
Intercept	0.468	0.068	2.1×10^{-11}	0.350	0.213	0.101	0.402	0.227	0.077	0.387	0.223	0.084
Control-case	0.188	0.033	2.4×10^{-8}	0.277	0.042	1.1×10^{-10}	0.223	0.053	3.6×10^{-5}	0.154	0.047	0.001
Controls × time	0.000	0.002	0.984	0.000	0.003	0.999	0.000	0.003	0.973	0.000	0.003	0.938
Cases × time	0.009	0.002	8.0×10^{-6}	0.016	0.004	2.4×10^{-5}	0.010	0.005	0.030	0.002	0.004	0.559

Abbreviations: CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma.

[a]Concentration data were log transformed and winsorized prior to modeling.

[b]Difference for immune marker concentration between controls and cases (positive β indicates higher concentrations for cases).

[c]Interaction term for controls with time (positive β indicates increasing concentration towards diagnosis of the incident case; age effect).

[d]Interaction term for cases with time (positive β indicates increasing concentration towards diagnosis).

Associations between B-cell lymphoma risk and marker levels were found to be stronger among the repeated samples than the baseline samples for all markers investigated, except CXCL13 (Table 2). Subgrouping of samples by time between blood draw and diagnosis revealed that elevated concentrations of CXCL13, sCD23, sCD27, and sCD30 were associated with B-cell lymphoma risk in samples collected 15 to 25 years before diagnosis. Although, associations with lymphoma risk were more pronounced in samples collected 0 to 3 years before diagnosis (Table 2).

Linear mixed model analyses showed that lymphoma cases had higher concentrations of all five immune markers compared with controls (Table 3). Among controls, there was no association between marker levels and time, indicating that their levels were temporally stable, except for sTNF-R1 ($\beta = 0.003$, $P = 0.003$). Intraclass correlation coefficients between baseline, and repeated samples varied between moderate for sCD30 (0.6) and high for sCD23 and sCD27 (0.9) among controls. B-cell lymphoma cases, in contrast, displayed increasing levels over time for all markers (Table 3; Fig. 1A and B), which was also corroborated in case-only analyses (Supplementary Table S1). Indolent subtypes displayed the most pronounced difference between cases and controls over time (as evaluated by the interaction term between case–control status and time), with increasing marker concentrations among future cases towards diagnosis. Almost all marker concentrations increased over time among CLL (sCD23, sCD27, sCD30) and follicular lymphoma (CXCL13, sCD23, sCD27 and sCD30), where the strongest association between marker level and time was observed for sCD23 and CLL ($\beta = 0.025$, $P = 5.470 \times 10^{-13}$). In contrast, among DLBCL, the major aggressive lymphoma subtype, only CXCL13 displayed significantly increasing plasma levels over time ($\beta = 0.014$, $P = 5.440 \times 10^{-4}$; Table 3). To investigate this heterogeneity among subtypes further, case-only analyses including aggressive and indolent B-cell lymphoma subtypes were performed. Indolent subtypes displayed higher immune marker concentrations compared with aggressive subtypes for sTNF-R1 ($\beta = 0.052$, $P = 0.026$), sCD23 ($\beta = 0.337$, $P = 1.530 \times 10^{-7}$), and sCD27 ($\beta = 0.127$, $P = 0.021$). Plasma levels for sCD23 ($\beta = 0.021$, $P = 0.001$), sCD27 ($\beta = 0.011$, $P = 0.030$), and sCD30 ($\beta = 0.011$, $P = 0.028$) increased over time among indolent cases, while remaining temporally stable among aggressive subtypes (Table 4).

To characterize how baseline measures and changes over time (i.e., slope) were associated with lymphoma risk, these variables were modeled by multivariable conditional logistic regression. We found that both concentration at baseline and slope were significantly associated with lymphoma risk for CXCL13, sCD23, sCD27, and sCD30 (Table 5). Subtype-specific analyses showed that the association between risk and slope in general was stronger among indolent than among aggressive B-cell lymphoma subtypes, particularly for sCD23 and sCD27. Among aggressive lymphoma, the association between DLBCL risk and marker slope was restricted to CXCL13 (Table 5).

To reduce the influence of undiagnosed disease on immune marker slopes, we performed sensitivity analyses for the association between B-cell lymphoma risk and immune marker slopes (adjusted for the baseline measure) by excluding samples collected close to diagnosis ($\leq$3 years). These results remained principally the same, although for sCD30, the association between slope and risk did not reach statistical significance ($P = 0.161$; data not shown). Furthermore, we compared the immune marker trajectories of B-cell lymphoma cases whose repeat sample was collected $\geq$6 years prior to diagnosis with those whose repeat sample was collected $\leq$3 years

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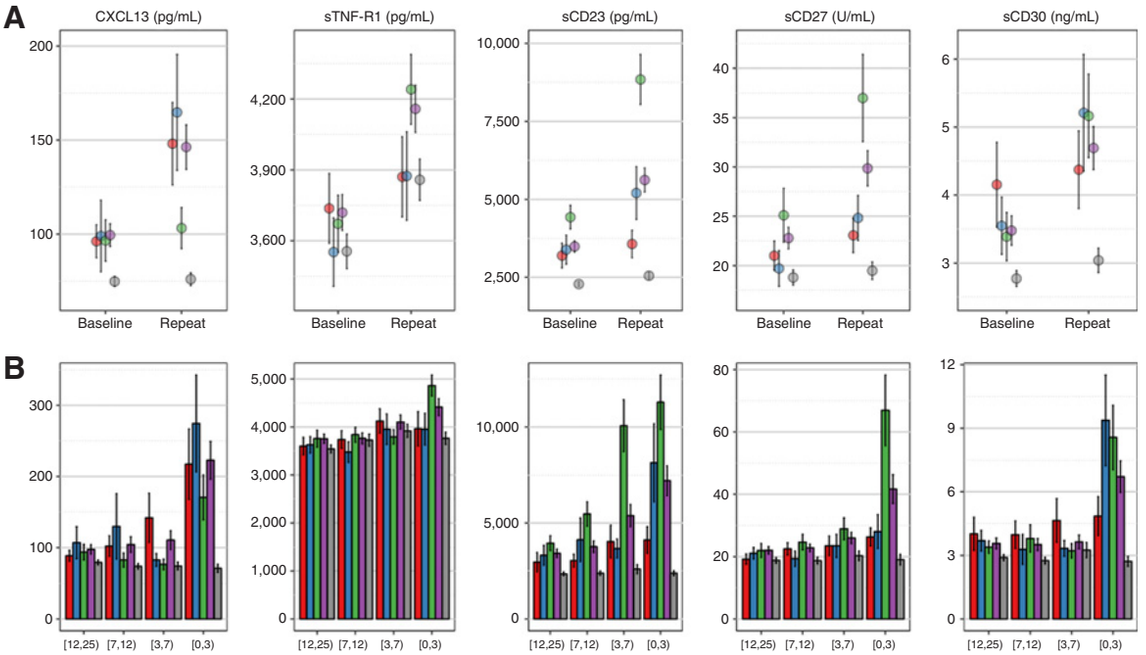

Figure 1.

Immune marker concentrations. Average blood concentrations in different groups are plotted (winsorized concentrations). **A,** Observations are grouped by sampling occasion, where baseline represents the first sampling (13.2 ± 4.4 years prior to diagnosis) and repeated represents the second sampling (5.5 ± 4.0 years prior to diagnosis). **B,** Observations are grouped by how long prior to diagnosis (years) the sample was drawn, regardless of it being the baseline or repeated sample. Error bars, SEM. Diagnostic groups are represented by different colors: diffuse large B-cell lymphoma (red), follicular lymphoma (blue), chronic lymphocytic leukemia (green), B-cell lymphoma (purple), matched controls (gray). [ ), greater or equal to n years and less than n years.

prior to diagnosis. These analyses showed that marker slopes for CXCL13, sTNF-R1, sCD27 and sCD30 were significantly steeper among cases with repeated blood sample collection close to diagnosis (≤3 years); CXCL13 (OR = 6.2, $P_{trend} = 0.002$), sTNF-R1 (OR = 4.1, $P_{trend} = 0.041$), sCD23 (OR = 1.0, $P_{trend} = 0.756$), sCD27 (OR = 2.1, $P_{trend} = 0.030$), and sCD30 (OR = 4.6, $P_{trend} = 0.004$; OR = 4th vs. 1st Q; Supplementary Table S2).

To examine possible multicollinearity between markers, all four immune markers that displayed significant associations between risk and both slope and baseline concentration in the main analyses (including all samples) were modeled together in a multivariable logistic regression analysis. In this analysis, measures for CXCL13 and sCD23 remained significant; CXCL13 ($OR_{Baseline} = 10.1$; $P_{trend} = 2.750 \times 10^{-4}$; $OR_{Slope} = 2.3$, $P_{trend} = 0.020$), sCD23 ($OR_{Baseline} = 5.9$, $P_{trend} = 0.005$; $OR_{Slope} = 3.3$, $P_{trend} = 2.787 \times 10^{-4}$), sCD27 ($OR_{Baseline} = 3.7$, $P_{trend} = 0.125$; $OR_{Slope} = 3.4$, $P_{trend} = 0.078$), and sCD30 ($OR_{Baseline} = 0.6$, $P_{trend} = 0.492$; $OR_{Slope} = 0.9$, $P_{trend} = 0.948$; OR = 4th vs. 1st Q).

Discussion

B-cell–stimulatory markers have been investigated in longitudinal studies in AIDS-associated B-cell lymphoma (20–22). Among the general population, this is to the best of our knowledge the first prospective study reporting on B-cell activation markers and future risk of developing B-cell lymphoma using repeated prediagnostic blood samples. Our results for risk estimates are consistent with a meta-analyses on circulating B-cell activation markers and future lymphoma risk (9). We here extend

Table 4. Linear mixed effect modeling (case-only analysis for aggressive and indolent B-cell lymphoma cases)

	Aggressive/indolent B-cell lymphoma ($N = 164$)		
Parameter[a]	**β**	**SE**	***P***
CXCL13			
Intercept	1.757	0.427	6.560×10^{-5}
Aggressive-indolent[b]	0.025	0.067	0.712
Aggressive × time[c]	0.009	0.006	0.152
Indolent × time[c]	0.010	0.006	0.073
sTNF-R1			
Intercept	3.343	0.162	$<1.0 \times 10^{-15}$
Aggressive-indolent	0.052	0.023	0.026
Aggressive × time	−0.001	0.002	0.961
Indolent × time	0.003	0.002	0.155
sCD23			
Intercept	3.933	0.466	4.090×10^{-14}
Aggressive-indolent	0.337	0.062	1.530×10^{-7}
Aggressive × time	0.005	0.007	0.450
Indolent × time	0.021	0.006	0.001
sCD27			
Intercept	1.004	0.387	0.011
Aggressive-indolent	0.127	0.055	0.021
Aggressive × time	0.003	0.006	0.553
Indolent × time	0.011	0.005	0.030
sCD30			
Intercept	0.539	0.377	0.155
Aggressive-indolent	0.080	0.061	0.189
Aggressive × time	0.002	0.006	0.708
Indolent × time	0.011	0.005	0.028

[a]Concentration data were log transformed and winsorized prior to modeling.
[b]Difference for immune marker levels between aggressive and indolent BCL subtypes (positive β indicates higher concentrations for indolent subtypes).
[c]Interaction term for aggressive or indolent BCL subtypes with time to diagnosis (positive β indicates increasing immune marker levels towards diagnosis).

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Table 5. Multivariable logistic regression for B-cell lymphoma risk and major subtypes adding measures for baseline and the annual change (slope)

		B-cell lymphoma		CLL		Follicular lymphoma		DLBCL	
Analyte measures[a]	**$N_{Controls}$**	***N***	**OR[b] (95% CI)**	***N***	**OR[c] (95% CI)**	***N***	**OR[c] (95% CI)**	***N***	**OR[c] (95% CI)**
CXCL13 (pg/mL)									
Baseline									
≤50.02	42	31	Ref	13	Ref	5	Ref	6	Ref
50.03–67.82	42	37	1.41 (0.66–3.01)	9	0.70 (0.26–1.89)	8	1.64 (0.44–6.07)	11	1.76 (0.54–5.70)
67.83–86.79	42	25	0.86 (0.36–2.03)	8	0.69 (0.24–1.93)	6	1.09 (0.26–4.64)	3	0.59 (0.13–2.73)
≥86.80	42	75	6.14 (2.42–15.58)	20	2.30 (0.83–6.39)	11	2.39 (0.58–9.79)	22	4.81 (1.42–16.32)
P_{trend}[d]			1.685×10^{-5}		0.050		0.187		0.004
Slope									
≤−2.32	42	33	Ref	11	Ref	2	Ref	10	Ref
−2.31–0.00	42	27	1.19 (0.53–2.69)	12	1.44 (0.51–4.08)	3	1.65 (0.23–11.89)	5	0.99 (0.26–3.80)
0.01–1.70	42	29	1.44 (0.62–3.33)	7	0.84 (0.27–2.62)	5	2.94 (0.48–18.08)	7	1.37 (0.39–4.80)
≥1.71	42	79	4.43 (2.02–9.71)	20	2.44 (0.94–6.32)	20	14.44 (2.81–74.11)	20	3.08 (1.07–8.89)
P_{trend}			3.905×10^{-5}		0.073		4.558×10^{-5}		0.018
sTNF-R1 (pg/mL)									
Baseline									
≤2,953	42	40	Ref	11	Ref	6	Ref	12	Ref
2,954–3,436	42	35	1.00 (0.52–1.94)	9	0.82 (0.29–2.30)	8	1.46 (0.43–4.99)	9	0.76 (0.26–2.22)
3,437–4,007	42	37	1.06 (0.55–2.05)	13	1.22 (0.45–3.26)	10	1.91 (0.55–6.64)	4	0.25 (0.07–0.96)
≥4,008	42	56	2.12 (0.94–4.81)	17	1.74 (0.63–4.78)	6	1.66 (0.42–6.57)	17	1.04 (0.37–2.93)
P_{trend}			0.091		0.123		0.766		0.847
Slope									
≤−18.77	42	36	Ref	9	Ref	6	Ref	13	Ref
−18.76–35.14	42	43	1.54 (0.76–3.10)	11	1.33 (0.44–4.08)	12	2.33 (0.67–8.11)	9	0.81 (0.24–2.66)
35.15–95.27	42	37	1.27 (0.65–2.48)	8	0.99 (0.32–3.08)	7	1.27 (0.35–4.60)	7	0.38 (0.12–1.22)
≥95.28	42	52	1.86 (0.92–3.75)	22	2.79 (1.06–7.32)	5	0.94 (0.25–3.57)	13	0.73 (0.26–2.03)
P_{trend}			0.163		0.025		0.599		0.516
sCD23 (pg/mL)									
Baseline									
≤1,525	42	16	Ref	3	Ref	2	Ref	4	Ref
1,526–2,133	43	29	2.52 (0.99–6.39)	5	1.98 (0.34–11.43)	5	2.45 (0.41–14.59)	8	2.57 (0.58–11.47)
2,134–2,768	42	36	2.66 (1.03–6.84)	7	2.64 (0.45–15.45)	10	4.95 (0.92–26.60)	13	5.21 (1.22–22.33)
≥2,769	42	87	5.70 (2.41–13.48)	35	19.36 (3.84–97.55)	13	10.19 (1.77–58.71)	17	6.76 (1.59–28.70)
P_{trend}			8.256×10^{-6}		1.509×10^{-6}		0.002		0.004
Slope									
≤−25.89	42	30	Ref	4	Ref	4	Ref	14	Ref
−25.88–5.08	42	23	0.79 (0.33–1.88)	1	0.49 (0.05–5.25)	4	1.08 (0.22–5.39)	6	0.89 (0.26–3.04)
5.09–58.98	43	23	0.76 (0.31–1.86)	3	1.07 (0.19–6.18)	6	1.55 (0.35–6.91)	10	0.90 (0.30–2.74)
≥58.99	42	92	3.35 (1.65–6.80)	42	28.14 (6.82–116.16)	16	6.00 (1.53–23.52)	12	1.00 (0.36–2.78)
P_{trend}			1.206×10^{-5}		7.279×10^{-10}		0.001		0.848
sCD27 (U/mL)									
Baseline									
≤11.87	42	20	Ref	6	Ref	7	Ref	4	Ref
11.88–17.14	42	38	2.90 (1.14–7.35)	15	1.90 (0.61–5.88)	3	0.51 (0.11–2.28)	9	1.82 (0.46–7.14)
17.15–23.71	42	56	5.03 (1.85–13.64)	11	1.43 (0.44–4.62)	11	1.88 (0.60–5.94)	18	4.83 (1.37–17.07)
≥23.72	42	54	7.19 (2.27–22.77)	18	3.35 (1.04–10.79)	9	1.14 (0.29–4.46)	11	2.64 (0.66–10.57)
P_{trend}			2.758×10^{-4}		0.024		0.161		0.068
Slope									
≤−0.29	42	41	Ref	6	Ref	8	Ref	13	Ref
−0.28–0.07	42	25	0.99 (0.45–2.18)	4	1.10 (0.26–4.69)	6	0.70 (0.18–2.74)	8	0.78 (0.24–2.57)
0.08–0.43	42	25	0.97 (0.43–2.20)	10	2.64 (0.75–9.27)	3	0.34 (0.07–1.74)	5	0.53 (0.15–1.89)
≥0.44	42	77	2.84 (1.36–5.92)	30	6.70 (2.27–19.78)	13	1.64 (0.51–5.24)	16	1.43 (0.52–3.92)
P_{trend}			2.223×10^{-4}		1.342×10^{-5}		0.065		0.256
sCD30 (ng/mL)									
Baseline									
≤1.97	42	33	Ref	11	Ref	5	Ref	7	Ref
1.98–2.39	42	28	0.92 (0.44–1.92)	8	0.71 (0.24–2.11)	5	0.53 (0.12–2.29)	6	0.72 (0.20–2.66)
2.40–3.11	42	45	1.24 (0.58–2.67)	11	0.81 (0.29–2.27)	8	0.93 (0.24–3.68)	13	1.14 (0.35–3.68)
≥3.12	42	62	2.87 (1.27–6.48)	20	2.43 (0.89–6.68)	12	1.36 (0.35–5.23)	16	1.83 (0.56–5.96)
P_{trend}			3.663×10^{-4}		0.011		0.039		0.029
Slope									
≤−0.06	42	40	Ref	8	Ref	9	Ref	14	Ref
−0.05–0.00	42	24	0.71 (0.34–1.48)	6	1.23 (0.35–4.33)	3	0.34 (0.07–1.53)	6	0.63 (0.17–2.29)
0.01–0.08	42	25	1.02 (0.46–2.26)	8	1.39 (0.41–4.72)	4	0.43 (0.10–1.91)	5	0.47 (0.13–1.75)
≥0.09	42	79	2.86 (1.46–5.60)	28	5.85 (2.09–16.42)	14	1.99 (0.67–5.92)	17	1.73 (0.61–4.92)
P_{trend}			0.001		4.766×10^{-5}		0.038		0.239

Abbreviations: CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma.

[a]Analyte measures for baseline and slope divided into quartiles based on concentrations among controls.

[b]ORs calculated by conditional logistic regression adjusted for body mass index and smoking status.

[c]ORs calculated by nonconditional logistic regression adjusted for sex, age, sample dates, analysis plate, body mass index, and smoking status.

[d]Two-sided *P* values were calculated by including median values of analyte quartiles as continuous variable.

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these findings to show that independent of baseline marker concentration, the risk also is associated with an increase in marker concentrations over time (slope).

Beside the observed dynamic trends for B-cell activation markers among future B-cell lymphoma cases, the data suggest a marked increase for biomarker slopes towards diagnosis (Fig. 1B; Supplementary Table S2). These findings could not have been predicted by previous studies using single blood samples (4–11). Our data show the presence of individual trajectories that may be indicative of the disease or disease process.

The observed slopes of the measured B-cell activation markers may be viewed from two different perspectives; they could either be caused by early stages of disease, or could be an etiologic factor reflecting progression to clinical disease. In support of the first view, we found that the increase was more prominent among indolent lymphoma subtypes than among aggressive subtypes. Given the long latency time of indolent lymphoma, it is expected that the actual onset of disease is years before diagnosis. This applies in particular to sCD23 and sCD27, as both have been associated with tumor load in CLL patients (23, 24). Furthermore, it is plausible that increasing levels of CXCL13 might be caused by undiagnosed disease among future follicular lymphoma patients, considering that we did not observe elevated levels at the baseline measure and as it has previously been shown that CXCL13 is produced by follicular lymphoma cells (25). Assuming that increasing levels of B-cell activation markers are caused by early stages of disease, these markers could potentially be utilized in clinical lymphoma management, similar to high frequency t(14;18) that has been suggested as an early blood-based biomarker for follicular lymphoma (26).

On the other hand, the observed B-cell activation marker increase towards diagnosis may be interpreted as etiologic involvement in B-cell lymphoma development. The concentration increase over time may reflect biological processes involved in the onset of the disease or be a measure of the allostatic load on the B-cell compartment. This is supported by recent observations that varying levels of various immune markers, many belonging to the adaptive immune system, are influenced by nonheritable factors such as the environment (27). High blood concentrations of CXCL13, sTNF-R1, sCD23, sCD27, and sCD30 have been associated to disease states related to immune system activation, such as autoimmune diseases, hepatitis, and HIV infection (28–32). Another plausible explanation for the observed marker increase over time may thus be longstanding chronic inflammation, or infection leading to sustained B- or T-cell activation, and ultimately resulting in lymphoma development (33).

To reduce the influence of undiagnosed disease on the observed marker trajectories, we performed sensitivity analyses excluding samples collected close to diagnosis, and found that the results remained principally the same. In addition, we observed a clear slope for CXCL13 among DLBCL patients, arguing against that increasing marker concentrations in general are attributable to undiagnosed disease, considering that the median survival of DLBCL is expected to be only a few months if left untreated (34).

As investigated markers were correlated, it may be possible that one marker serves as a surrogate of another. When baseline and slope measures of all markers were modeled together, neither baseline nor slope measures for sCD27 and sCD30 were associated with B-cell lymphoma risk which may be explained by the highest observed but still weak to moderate inter-marker correlation between sCD23 and sCD27 ($r_S = 0.27$), and sCD23 and sCD30 ($r_S = 0.32$).

Our study had some limitations. Given the high heterogeneity of B-cell lymphoma, the statistical power was limited when performing subanalyses on histologic subtypes. Some bias may have been introduced due to inaccurate self-reporting of included covariates, such as BMI and smoking status. Another drawback was the lack of general lymphoma risk factor data. The prevalence of HIV, one of the strongest lymphoma risk factors (35), is expected to be as low as 0.15% among the general population in Sweden (36). Thus, we do not expect this to influence our results. On the other hand, there are several strengths of our study, including the analyses of repeated blood samples, adequate case–control matching, good blood sample quality, and the same standardized biobank procedures for samples collected throughout the 30-year study period.

In conclusion, increased B-cell activation marker levels, observed early in life across different lymphoma subtypes, suggest a role of B-cell activation in B-cell lymphoma development at early stages. These perturbations may reflect a constitutional predisposition with shared underlying mechanisms for both indolent and aggressive lymphoma subtypes. Observed dynamic trajectories for these markers seem to be subtype-specific and mainly driven by indolent lymphoma. Therefore, they may reflect early progression of undiagnosed disease and could potentially be utilized in screening and monitoring of indolent lymphoma. Among aggressive lymphoma, however, DLBCL development seems to be driven by both increased B-cell activation early in life, as well as by progressive CXCL13 levels over time. Studies investigating the clinical impact of these B-cell activation markers, as recently shown for CXCL13 blood levels at AIDS lymphoma diagnosis (37), are required.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: F. Späth, I.A. Bergdahl, R. Vermeulen, B. Melin
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): F. Späth, E.J.M. Krop, I.A. Bergdahl, R. Vermeulen, B. Melin
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): F. Späth, C. Wibom, R. Vermeulen, B. Melin
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