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Elevated serum sCD23 and sCD30 up to two decades prior to diagnosis associated with increased risk of non-Hodgkin lymphoma

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Letter to the Editor

Conditions involving severe immune dysregulation are strong risk factors for non-Hodgkin lymphoma (NHL).[1] However, it is unclear whether subclinical immunologic perturbations influence NHL risk. We and other investigators have recently reported NHL associations with elevated pre-diagnostic serum concentrations of the immune markers soluble CD23 (sCD23), sCD27, sCD30, B cell attracting chemokine-1 (BCA1), soluble tumor necrosis factor receptor-2 (sTNFR2), and soluble vascular endothelial growth factor receptor-2 (sVEGFR2).[2–7] While these findings support a role for immunologic effects in lymphomagenesis, the relatively short duration of follow-up after phlebotomy in these studies (10–13 years) limits the ability to rule out reverse causation as an explanation, given the potential for developing lymphomas to express these markers or indirectly affect their expression. Investigations within cohorts with longer follow-up time are needed to clarify the temporal nature of these associations. To that end, we conducted a nested case-control study investigating serum levels of these analytes and NHL diagnosed up to 23 years after phlebotomy within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a cohort with banked fasting serum from 29 133 male Finnish smokers.

The ATBC Study was approved by institutional review boards of the National Cancer Institute and the National Public Health Institute of Finland; written informed consent was obtained from all participants.[8] We identified 272 first-primary NHL cases diagnosed 2+

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

M.P.P. led the study design and statistical analysis, and prepared the manuscript; Q.L., S.J.W., J.V., D.A., and N.R. contributed to the study design; T.J.K. conducted the assays; L.A.P. supervised this laboratory work; A.H. oversaw the data formatting and quality control checks of the assay data; J.N.H. contributed to the statistical analysis; all authors provided intellectual input into preparation of the manuscript.

years after phlebotomy through 2009 via the Finnish Cancer Registry. Fifty-three multiple myeloma cases were also selected but excluded from this report. We individually matched controls (N=325) to cases by baseline age (+/− 2 years), phlebotomy date (+/− 30 days), and number of previous specimen thaws from among participants alive and cancer-free at case diagnosis. Serum concentrations of the analytes were measured by ELISA (sCD23, sCD27, sCD30; Bender Medsystems, Burlingame, CA, USA) and Luminex-based assay (BCA1, sTNFR2, sVEGFR2; EMD Millipore, Billerica, MA, USA). For sCD23, a 1:2 dilution was performed for batches 3 onward to account for low serum volumes for many of the test samples; statistical analyses of this analyte were restricted to these batches. Sera from case-control pairs were assayed consecutively within batches along with blinded quality-control pool replicates (n = 32). Measurements were highly reproducible, with coefficients of variation for log-transformed concentrations <5%.

Odds ratios (ORs) and 95% confidence intervals (CIs) for analyte concentrations (grouped into three categories using control tertiles as cutpoints unless otherwise specified; see Table 1) were computed using conditional logistic regression adjusting for cigarette pack-years. Trend tests were conducted by modeling intra-category medians as a continuous parameter. Analyses were conducted both overall and stratified across three follow-up periods: 2-<8 years (85 cases, median follow-up 5.4 years), 8-<15 years (101, 11.3), and 15-<24 years (86, 19.8). Polytomous regression models were used to compute associations with the two most common histologic subtypes, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; N=74) and diffuse large B-cell lymphoma (DLBCL; N=60), adjusting for age, year of phlebotomy, number of prior controlled thaws, and cigarette pack-years. Analyses of other NHL subtypes were limited by sparse numbers and are not reported. Analyses stratified by pack-years were conducted using unconditional logistic regression modeling with adjustment for age, year of phlebotomy, and number of prior controlled thaws. The statistical analysis was performed using SAS version 9.2. All statistical tests were two-sided.

Cases had higher cigarette pack-years than controls (37.0 vs. 33.5 respectively; P=0.02), but were otherwise comparable for age, body mass index, and education level (Supplemental Table 1). sCD27, sCD30, BCA1, sTNFR2, and sVEGFR2 were moderately correlated with one another among controls, with Spearman rank coefficients ranging from 0.21 (BCA1-sVEGFR2) to 0.70 (sTNFR2-sVEGFR2), whereas sCD23 levels were not correlated with other analytes (r = −0.14 to 0.09).

As summarized in Table 1, cases had higher serum levels than controls of sCD23 (high category vs. low: OR = 2.4, 95% CI = 1.5–3.8, P_{trend} = 0.0005), sCD27 (3.0, 1.8–4.9, P_{trend} < 0.0001), sCD30 (3.3, 1.9–5.5, P_{trend} < 0.0001), and sTNFR2 (2.0, 1.2–3.3, P_{trend} = 0.008). When these analytes were modeled simultaneously, associations remained for sCD23 (OR = 1.8, P_{trend} = 0.03), sCD27 (2.1, 0.006), and sCD30 (2.2, 0.02). Associations were apparent for cases diagnosed 15–23 years post-phlebotomy for sCD23 (5.1, 1.8–14.6, P_{trend} = 0.002) and sCD30 (3.7, 1.5–9.3, P_{trend} = 0.01), whereas associations with sCD27 and sTNFR2 were strongest for cases diagnosed 2-<8 years post-phlebotomy, and weaker or null in later follow-up periods. The NHL associations with sCD23 and sCD30 did not significantly differ across categories of cigarette pack-years (Supplemental Table 2). We observed little evidence of association with BCA1 or sVEGFR2 (Supplemental Table 3).

sCD23 and sCD30 were associated with DLBCL, both overall (sCD23: OR = 2.2, 95% = 1.1–4.4, P_{trend} = 0.03; sCD30: 3.9, 1.8–8.2, P_{trend} = 0.0001) and in later follow-up periods (Figure 1; results for all analytes in Supplemental Table 4). sCD23 was strongly associated with CLL/SLL (5.1, 2.6–10.1, P_{trend} = 0.0001), particularly for cases diagnosed within 2–<8 years (7.3, 2.1–24.9, P_{trend} = 0.0004) and 8–<15 years (7.8, 2.5–24.3, P_{trend} = 0.0002) post-phlebotomy. sCD30 was not significantly associated with CLL/SLL.

Our findings are consistent with the hypothesis that circulating sCD23 and sCD30, associated with NHL risk as many as 15–23 years after phlebotomy, are biomarkers reflective of immunologic mechanisms contributing to lymphomagenesis. sCD23 and sCD30, the soluble forms of the surface receptors CD23 and CD30, have been proposed to be informative surrogate markers of B cell activation.[9] Both CD23, a low-affinity IgE receptor, and sCD23 have been shown to induce B cell stimulatory effects.[10,11] CD30 is preferentially expressed by activated type-2 T cells, which produce cytokines enhancing B cell activation.[12,13] Sustained B cell activation may contribute to NHL development by increasing the potential for unrepaired lymphomagenic genetic errors.

We cannot rule out the possibility of occult disease influencing some of our findings, particularly for indolent malignancies such as CLL. Indeed, we observed strong sCD23 associations for CLL/SLL diagnosed closer in time to phlebotomy which may be at least partly disease-induced, as circulating sCD23 in CLL patients has been associated with tumor burden.[14] However, our sCD23 findings for the more aggressive DLBCL are consistent with etiologic effects, given the consistency in associations across follow-up periods and especially the strong risk present even among cases diagnosed 15–23 years after phlebotomy. The weaker NHL associations for sCD27 and sTNFR2 ≥8 years post-phlebotomy may reflect disease-induced effects, odds ratio attenuation due to a decline in representativeness of one-time analyte measurements as surrogates for usual levels, or both.

The generalizability of these findings is questionable, given that the study population consisted entirely of male Finnish heavy smokers. However, similar NHL and subtype associations with sCD23 and sCD30 have previously been reported (although with fewer years of follow-up) in population-based cohorts that include women (including one all-female cohort) and non-smokers.[3,4,6]

Our findings raise the possibility that serum sCD23 and sCD30 may hold promise as surrogate endpoints for cross-sectional studies of suspected B-cell-stimulative risk factors. It is also possible, though speculative, that these markers may have future clinical value in developing NHL risk prediction models. In particular, given the strong association with CLL/SLL risk observed for elevated sCD23 in serum collected ≤15 years before diagnosis, there is a need to investigate whether elevated levels of this marker are predictive of future progression to CLL among patients with monoclonal B cell lymphocytosis (MBL), an asymptomatic precursor condition to this malignancy.[15] Studies addressing these questions, particularly using serially collected specimens, are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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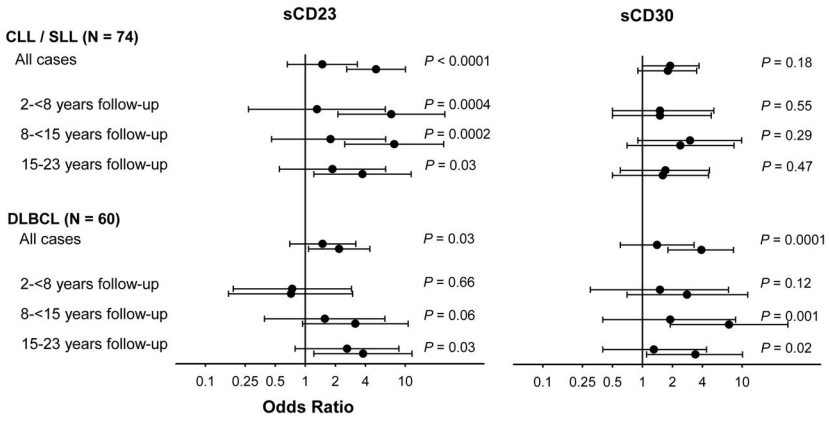

Figure 1. Associations between serum sCD23 and sCD30 and future risk of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and diffuse large B cell lymphoma (DLBCL), overall and by period of follow-up

Odds ratios (represented by circles) and corresponding 95% confidence limits (represented by vertical bars) are shown from comparisons of medium (middle circle) and high (bottom circle) vs. low (reference; top circle) analyte concentrations. The analyte category cutpoints are provided in Table 1. Odds ratios computed through polytomous regression with adjustment for age, year of phlebotomy, number of prior controlled thaws, and cigarette pack-years. *P*-values are from test of trend.

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Table 1

Associations between serum sCD23, sCD27, sCD30, and sTNFR2 and future NHL risk (overall and by follow-up period) in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

				Stratified by Follow-up Time From Phlebotomy To Case Diagnosis					
		All Cases and Controls		2–<8 Years		8–<15 Years		15–23 Years	
		(272 Cases, 325 Controls)		(85 Cases, 105 Controls)		(101 Cases, 118 Controls)		(86 Cases, 102 Controls)	
Analyte, Units	**Category[a]**	**N_{Ca}[b]/N_{Cont}**	**OR[c] (95% CI)**	**N_{Ca}/N_{Cont}**	**OR (95% CI)**	**N_{Ca}/N_{Cont}**	**OR (95% CI)**	**N_{Ca}/N_{Cont}**	**OR (95% CI)**
sCD23[d], U/ml	≤ 3.125	87/139	1.0	24/35	1.0	35/48	1.0	28/56	1.0
	3.126 – 53.561	65/68	1.5 (0.9–2.3)	20/21	1.8 (0.8–4.3)	26/26	1.3 (0.6–2.7)	19/21	1.7 (0.7–4.0)
	> 53.561	84/69	2.4 (1.5–3.8)	28/27	2.1 (0.9–5.1)	28/27	1.5 (0.7–3.2)	28/15	5.1 (1.8–14.6)
			P_{trend} = 0.0005		P_{trend} = 0.12		P_{trend} = 0.30		P_{trend} = 0.002
sCD27, U/ml	≤ 44	56/111	1.0	10/31	1.0	24/44	1.0	22/36	1.0
	45 – 61	94/112	2.0 (1.2–3.1)	23/37	3.9 (1.2–12.4)	27/33	1.3 (0.6–2.9)	44/42	2.0 (0.9–4.1)
	> 61	121/102	3.0 (1.8–4.9)	52/37	8.4 (2.6–27.8)	50/41	2.7 (1.3–5.7)	19/24	1.4 (0.6–3.5)
			P_{trend} < 0.0001		P_{trend} = 0.0005		P_{trend} = 0.007		P_{trend} = 0.46
sCD30, pg/ml	≤ 19 295	52/107	1.0	13/29	1.0	20/36	1.0	19/42	1.0
	19 296 – 29 775	105/111	2.5 (1.5–4.2)	31/33	3.5 (1.3–9.5)	38/43	2.1 (0.9–4.7)	36/35	2.5 (1.1–5.7)
	> 29 775	114/106	3.3 (1.9–5.5)	41/43	4.1 (1.4–11.8)	43/38	2.6 (1.1–6.1)	30/25	3.7 (1.5–9.3)
			P_{trend} < 0.0001		P_{trend} = 0.03		P_{trend} = 0.04		P_{trend} = 0.01
sTNFR2, pg/ml	≤ 5 634.40	67/108	1.0	11/28	1.0	24/36	1.0	32/44	1.0
	5 634.41 – 7 841.82	93/110	1.6 (1.0–2.6)	31/32	3.2 (1.2–8.4)	36/42	1.3 (0.6–2.8)	26/36	1.1 (0.4–2.5)
	> 7 841.82	111/107	2.0 (1.2–3.3)	43/45	3.6 (1.2–10.4)	41/40	1.8 (0.8–4.1)	27/22	1.5 (0.6–3.4)
			P_{trend} = 0.008		P_{trend} = 0.04		P_{trend} = 0.13		P_{trend} = 0.33

NHL indicates non-Hodgkin lymphoma; N_{Ca}, number of cases; N_{Cont}, number of controls; OR, odds ratio; CI, confidence interval.

[a] sCD23 categorized as ≤ assay limit of detection, ≤ the median among controls, and > control median. Other analytes categorized using tertiles among controls as cutpoints.

[b] Case frequencies do not include one case without assay data for the four analytes shown in this table.

[c] ORs computed by conditional logistic regression with adjustment for cigarette pack-years.

[d] sCD23 analyses restricted to samples in batches 3 onward.