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Pre-diagnostic serum sCD27 and sCD30 in serial samples and risks of non-Hodgkin lymphoma subtypes

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Abstract

Elevated pre-diagnostic serum levels of the immune activation markers sCD27 and sCD30 have been associated with non-Hodgkin lymphoma (NHL). However, the use of a single sample per participant in these studies has limited etiologic inferences. We report findings, overall and by NHL subtype, from a case-control analysis (422 cases, 434 controls) within the Janus Serum Bank with two samples per subject collected on average five years apart. Chronic lymphocytic leukemia / small lymphocytic lymphoma (CLL/SLL) was associated with elevated sCD27 in the later, but not earlier, pre-diagnostic sample (odds ratio [OR] 4.2, 95% confidence interval [CI] 1.5-11.6 and 1.7, 0.7-4.7 per log increase respectively) in analyses adjusting for both analytes, while follicular lymphoma (FL) was associated with elevated sCD30 in both the later and earlier samples (OR 2.9, 95% CI 1.4-4.4 and 2.3, 1.2-4.4 respectively). CLL/SLL cases were significantly more likely than controls to have higher sCD27 in the later vs. earlier sample (OR 1.4, 95% CI 1.1-1.9 per standard deviation increase); no such difference in sCD30 was apparent for FL. In a joint analysis, NHL cases were more likely than controls to have below-median sCD27 in the earlier sample and above-median sCD27 in the later sample (OR 1.5, 95% CI 1.0-2.3). For sCD30, the association between sCD30 and FL was confined to subjects with above-median analyte levels in both samples (OR 2.5, 95% CI 1.1-5.9). Our findings are compatible with elevated sCD27 representing a disease-induced effect and sCD30 representing a marker of increased FL susceptibility.

Introduction

It is well established that severe immune dysfunction is a strong risk factor for non-Hodgkin lymphoma (NHL), a classification including several lymphoid malignancies mostly originating from B cells.[1] Whether more subtle immunologic effects affect the development of NHL in non-immunocompromised populations has been the focus of investigation within population cohorts using serologic measurements of cytokines and other immune

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markers. From these studies, elevated circulating levels of soluble CD27 (sCD27) and sCD30, markers of immune activation,[2] have been consistently associated with increased risk.[3-10] The study findings for these immune markers are compatible with an etiological role for underlying immunologic mechanisms in the development of NHL in the general population. However, a general limitation of past studies has been their reliance on a single pre-diagnostic specimen per subject; such single measurements may not be representative of long-term analyte levels and cannot capture systematic changes over time such as may be caused by a prodromal disease effect.

To extend research beyond single-sample studies, we recently investigated pre-diagnostic circulating levels of sCD27 and sCD30 among 83 cases and 102 controls enrolled in both the CLUE-I and CLUE-II cohorts, using two banked serum samples per participant collected fifteen years apart.[11] Although the small sample size limited our inferences, we observed case sCD27 levels to systematically increase closer to diagnosis, consistent with a disease effect, while consistently elevated sCD30 was associated with increased NHL risk, suggestive of a susceptibility marker.

Larger studies with repeated samples are needed to better characterize the prediagnosis temporal dynamics of these immune markers, both for overall NHL and individual disease subtypes. To that end, we report herein findings from a case-control investigation of 422 cases and 434 controls nested within the Janus Serum Bank featuring the measurement of sCD27 and sCD30 in paired serum samples collected several years apart. For this study we also expanded our investigation to include multiple myeloma (MM), a B cell malignancy that has rarely been the subject of past investigation for these immune markers.

Materials and Methods

The Janus Serum Bank, established in 1973, contains sera collected from persons undergoing health examinations in 17 of the 19 counties of Norway (N=289,089).[12] Approximately 75,000 subjects provided serum on two or more occasions. For our study we selected 497 histologically confirmed incident first-primary cases of NHL, including MM, from among health examination donors cancer-free at the time of their first donation (excluding non-melanoma skin cancer) identified through linkage to the Cancer Registry of Norway. We preferentially selected cases with two or more samples available or that had been included in a prior nested case-control study of NHL measuring serum organochlorine compounds.[13] Of the 103 cases included from the prior study, 62 had one banked sample and 41 had two or more samples. All of the remaining 394 selected cases that had not been included in the prior study had two or more samples available.

Controls (N=497) were individually matched to cases on age, availability of a second sample, blood draw date, sex, county of residence, and the number of times they have been included in previous studies. For cases included in the prior study of organochlorine compounds, we selected from among the controls in the original matched set from that study.

sCD27 and sCD30 were measured in duplicate by enzyme-linked immunosorbent assay (Bender Medsystems, Burlingame, USA). We excluded measurements from 3 of the 55 sCD30 plates (102 samples) due to problems with the standard curves, and from 42 samples with sCD30 measurements outside the range of the standard curve. Measurements from blinded quality control replicates (n=165) interspersed within and between batches demonstrated acceptable assay reproducibility, with intra-batch / total coefficients of variation of 3.2% / 13.4% and 4.7% / 13.7% for sCD27 and sCD30 respectively.

We restricted our analysis to subjects with two samples and, for cases, a diagnosis date at least five years after the second sample (422 cases, 434 controls) to minimize the potential for prodromal effects. Using conditional and unconditional logistic regression, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) relating the log-transformed analyte concentration from each sample to NHL adjusted for sex, age (years) at first sample collection, year of first sample collection, years between first and second sample and inclusion in the prior study of organochlorines. As we observed consistent results across models, only findings from unconditional models are reported. We tested for differences between samples in analyte ORs using a Wald statistic for a model parameter specifying the cross-product of sample-specific concentrations. We also computed ORs comparing cases and controls in relation to the difference in measured concentration between samples ($sample_2 - sample_1$) for each analyte. To further assess longitudinal changes in the analytes, we additionally analyzed a joint classification capturing dichotomized analyte levels in both samples, using the median concentration among controls as a cut-point . For these metrics we analyzed sCD27 and sCD30 both individually in separate models as well as simultaneously in a single model to calculate their effects independent of one another.

We also calculated ORs relating the analyte metrics to individual NHL subtypes (diffuse large B-cell lymphoma [DLBCL], chronic lymphocytic leukemia/small lymphocytic lymphoma [CLL/SLL], follicular lymphoma [FL], MM, marginal zone lymphoma (MZL), other or not otherwise specified histology [NOS]). As a sensitivity analysis we re-analyzed our results stratifying on time from second sample collection to case diagnosis (≤20 and >20 years). This study was approved by the regional committees for medical and health research ethics, Oslo, Norway, and was exempted from review by the institutional review board at the National Cancer Institute.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Selected subject characteristics are summarized in Table 1. Cases and controls had comparable distributions with regard to sex (~55% male), age at first sample collection (median: 42 years), calendar year of first sample collection (median: 1976) and years between samples (median: 5.0) The median length of follow-up to case diagnosis from the first and second samples was 27.3 and 21.2 years, respectively. The most common histologic subtypes were MM (N = 102; 24% of all cases), DLBCL (N = 76; 18%), CLL / SLL (N

= 71; 17%), FL (N = 44; 10%) and MZL (N = 22; 5%). The median age at diagnosis was 69 years overall, ranging between 66 and 74 years across subtypes (Supplemental Table 1). Among controls, natural log-transformed levels of sCD27 and sCD30 within the same sample were moderately correlated with one another (r = 0.35), while correlations across the paired samples for sCD27 and sCD30 were 0.61 and 0.24, respectively.

Findings from case-control analyses of immune marker levels in individual banked samples are provided in Table 2. While none of the immune markers were associated with overall NHL, associations with selected subtypes were observed. Elevated circulating levels of sCD27 in the second (i.e., more recent and closer to diagnosis) banked sample were associated with increased risk of CLL/SLL (OR 3.0, 95% CI 1.2-7.5 per log increase); for the first sample, the association with this subtype was weaker and non-significant (1.6, 0.7-3.7). These sCD27 associations with CLL/SLL remained in analyses simultaneously adjusting for sCD30 (1.7, 0.7-4.7 and 4.2, 1.5-11.6 for the first and second samples, respectively, although a test of differences in ORs across samples was not statistically significant. In addition, elevated sample-2 sCD27 was associated with reduced FL risk (0.3, 0.1-0.8). Elevated sCD30 was associated with increased FL risk in both the first and second samples, both in individual analyses (1.7, 1.0-3.1 and 2.2, 1.1-4.4 respectively) and controlling for sCD27 (2.3, 1.2-4.4 and 2.9, 1.4-4.4 respectively). For both sCD27 and sCD30, elevated levels in the second banked sample were associated with MZL (6.9, 1.5-31.1 and 3.3, 1.3-8.4 respectively), although these associations weakened after both analytes were modeled simultaneously (3.8, 0.7-22.3 and 2.4, 0.9-6.9). In analyses stratifying on case follow-up time, these associations were typically stronger for cases diagnosed within 20 years after the second sample collection (Supplemental Table 2); this was particularly evident for sCD27 and MZL, although confidence limits are very wide due to small case numbers.

In case-control analyses of the difference in analyte concentrations between samples (Table 3), CLL/SLL cases were more likely than controls to have a higher concentration of sCD27 in the second sample vs. the first, both with and without adjustment for sCD30 (OR 1.4, 95% CI 1.1-1.9 and 1.3, 1.0-1.7 per standard deviation increase respectively). This same pattern in sCD27 across samples was observed for MZL (OR 1.4, 9% CI 0.9-2.4 and 1.5, 1.0-2.3 with and without sCD30 adjustment), particularly for cases diagnosed within 20 years of the second sample (Supplemental Table 3). For sCD30, no clear differences in case levels across samples were apparent, other than suggestive evidence of higher sample-2 levels for DLBCL and MZL.

Results from comparisons of a joint classification of dichotomized sample-1 and sample-2 analyte concentrations between controls and cases are summarized in Table 4. Cases were more likely than controls to have below-median sCD27 levels in the first sample and above-median sCD27 in the second sample (“low / high”) vs. having below-median levels in each sample (“low / low”; OR 1.5, 95% CI 1.0-2.3). For sCD30, the low / high category was not associated with risk of NHL or individual subtypes. Instead, FL cases were significantly more likely than controls to have high sCD30 levels in both samples (“high / high”; 2.5, 1.1-5.9 and 2.1, 1.0-4.8 with and without sCD27 adjustment). In a joint analysis restricted to cases diagnosed within 20 years of the second sample, the sCD30 high / high association

with FL was stronger (OR 3.9, 95% CI 1.2-13.0 and 3.5, 95% CI 1.1-11.4 with and without sCD27 adjustment).

Discussion

In this nested case-control study investigating the relationship between serum concentrations of sCD27 and sCD30 and subsequent risk of NHL (overall and by subtype), we observed associations with CLL (for elevated sCD27), FL (sCD30), and MZL (sCD27 and sCD30) from analyses of individual sample measurements, as has been typically done in past studies. However, our use of serially collected pre-diagnostic sera also enabled us to evaluate longitudinal metrics of these analyte levels, providing further insight into the potential etiologic relevance of these markers. We hypothesized that case-control associations involving analytes increasing in concentration closer to diagnosis may be reflective of a disease-induced effect, while findings marked by relatively stable analyte concentrations over time would be suggestive of an etiologically relevant association. From our analyses involving both sample measurements, cases of CLL/SLL and MZL were more likely than controls to have higher levels of sCD27 (and, for MZL, sCD30) in the second vs. first sample. Additionally, in joint analyses of dichotomized measurements across samples, we found the low/high pattern for sCD27 to be more prevalent among NHL cases vs. controls, while for sCD30 the high / high pattern was associated with FL. These findings suggest that the observed associations for sCD27 may reflect disease-induced effects, and that elevated sCD30 may be a marker of FL susceptibility.

Our subtype-specific findings from analyses of individual sample measurements are consistent with those reported in a recent meta-analysis that investigated serum immune markers and NHL in past studies, where associations with sCD27 and sCD30 were strongest for CLL and FL respectively (MZL was not evaluated).[9] We also observed a similar pattern of associations for sCD27 and sCD30 in our earlier CLUE study with serial samples, although subtype-specific results were not informative due to the small sample size.[11] Another recent study of 170 NHL cases and 170 controls nested within the Swedish Health and Disease Study cohort also measured sCD27 and sCD30 in two banked serum samples collected several years apart.[10] In that study, both analytes were significantly higher on average closer to case diagnosis, including a strong, statistically significant increase for sCD27 and CLL and a weak, nominally significant increase for sCD30 and FL (MZL was not evaluated). This latter finding is inconsistent with our current report; one possible explanation may be the short time from second sample collection to case diagnosis in that study (mean 5 years), which would have been more sensitive to detecting proximal tumor-induced effects and less sensitive to capturing long-term, etiologically relevant associations.

sCD27 is a fragment of CD27, a member of the TNF receptor superfamily expressed on T-cells and a subset of B-cells that stimulates B-cell activation and immunoglobulin synthesis.[14, 15] We interpret our pattern of findings for sCD27 to be likely reflective of an underlying disease-induced effect from undiagnosed CLL/SLL and MZL. Clinical findings support this interpretation, as CD27 is typically expressed by MZL and CLL cells[16] and peridiagnostic serum sCD27 concentrations are positively correlated with tumor load.[17] We cannot however rule out an alternative, etiologically relevant explanation, whereby higher

case sample-2 levels compared to sample-1 levels reflect immune perturbations from the onset of an exposure or condition leading to lymphoma. This is particularly relevant in the case of MZL, extranodal cases of which are induced by chronic inflammation.[18]

sCD30 is the cleaved extracellular portion of CD30, a member of the TNF receptor superfamily expressed by a subset of activated T-cells which produce Th2-type cytokines stimulating B cell activation.[15, 19] Our pattern of results for sCD30 suggest that elevated levels of this analyte may be a marker of increased susceptibility to FL. FL is a malignancy arising from post-germinal center B lymphocytes characterized by the translocation t(14;18)(q43;q21), which confers resistance to apoptosis through BCL2 overexpression.[1] The etiology of FL is poorly understood; the only established risk factors to date include a personal history of selected autoimmune diseases, family history of lymphoma, and selected inherited genetic susceptibility variants identified from genome-wide association studies (GWAS).[1, 20, 21] The most striking GWAS finding for follicular lymphoma is the strong risk association with genetic variants on chromosome 6p21.32-33 within the major histocompatibility complex,[22-24] the strongest of which map to the gene *HLA-DRB1* encoding a human leukocyte antigen (HLA) protein that plays a central role in antigen presentation to T cells.[25] HLA-antigen interaction with T-cells is a necessary trigger for B-cell activation in the germinal center,[26] whereby B cells undergo the processes of clonal expansion, class switch recombination and somatic hypermutation. Chronic antigenic stimulation, such as with autoimmune disease, can lead to a sustained state of B cell activation that may increase the potential for secondary oncogenic hits to t(14;18)(q43;q21) cells through the introduction of genetic errors arising from these germinal center processes. We thus hypothesize that consistently elevated sCD30 is a marker for such high-risk states of persistent B cell activation, which may be modulated by HLA genetic variation.

Unlike with previous studies which involved a single sample collected typically closer to case diagnosis, we did not observe an association between sCD30 and DLBCL. We are unsure as to the explanation for this difference. We note however that in our analysis of changes in analyte concentrations between samples, we observed DLBCL to be more likely than controls to have a higher sCD30 concentration in the later vs. earlier sample (Table 3), although the difference did not reach statistical significance. In view of this finding, we speculate that it is possible that sCD30 associations with DLBCL observed in prior studies may at least partly reflect a disease-induced effect. In some analyses we observed elevated sCD30 to be associated with increased risk of MZL, although our findings from analyses involving measurements from both samples do not offer clear insight into whether the relationship reflects disease-induced or etiologic effects. More evidence from additional studies will be needed to clarify these subtype relationships.

A strength of this study is the use of serial banked samples collected several years apart and the long cancer follow-up after the second sample collection (median 21.2 years), enabling etiologically relevant longitudinal analyses of these analytes. To our knowledge, this project is the largest nested case-control study of circulating immune markers and NHL involving serial samples conducted to date, enabling our joint analysis of individual lymphoma subtypes. Another strength is our simultaneous modeling of sCD27 and sCD30 in our analysis to calculate analyte associations independent of one another, which has rarely

been investigated in past studies. In addition, this is to our knowledge the first study to report immune marker association findings for MZL. That said, our sample size limited our statistical power for individual subtypes, MZL in particular, and tests of interaction. Another limitation, in the context of our longitudinal analyses, was our use of two banked samples per subject; investigations involving three or more serial samples would provide richer data for capturing the temporal dynamics of these analytes.

In conclusion, our findings from this nested case-control study investigating serial measurements of immune activation markers and NHL risk suggest that associations with elevated circulating sCD27 may reflect disease-induced effects, particularly for CLL/SLL and MZL, and that elevated sCD30 may be a susceptibility marker for FL. Additional studies are needed to further investigate these and other immune markers in relation to individual subtypes, including MZL, as well as explore their interplay with other risk factors such as auto-immune diseases and HLA allelotypes. We are organizing a pooled analysis of relevant studies to pursue these objectives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CI	confidence interval
CLL	chronic lymphocytic leukemia
DLBCL	diffuse large B cell
FL	follicular lymphoma
GWAS	genome-wide association study
HLA	human leukocyte antigen
MM	multiple myeloma
MZL	marginal zone lymphoma
NHL	non-Hodgkin lymphoma
NOS	not otherwise specified
OR	odds ratio
sCD27	soluble CD27
sCD30	soluble CD30

SLL	small lymphocytic lymphoma

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Novelty and Impact:

Elevated pre-diagnostic serum levels of sCD27 and sCD30 have been associated with an increased risk of non-Hodgkin lymphoma. However, the use of a single sample per subject in past studies has limited etiologic inferences. Findings from this study, which included banked samples collected five years apart for 422 cases and 434 controls, suggest that sCD27 may be a marker of early disease, while sCD30 may be a marker of increased susceptibility to follicular lymphoma.

Table 1.

Characteristics of non-Hodgkin lymphoma cases and controls selected from the Janus Serum Bank.

	Cases (N=422)	Controls (N=434)
Sex		
Female	191 (45%)	198 (46%)
Male	231 (55%)	236 (54%)
Inclusion in previous nested case-control study of persistent organochlorine compounds		
Yes	28 (7%)	41 (10%)
No	394 (93%)	393 (91%)
Median year of first sample collection (min, max)	1976 (1973, 1988)	1976 (1973, 1988)
Median year of second sample collection (min, max)	1985 (1981, 2002)	1985 (1981, 2002)
Median age at first sample collection (min, max)	41.7 (22.6, 63.4)	41.6 (22.1, 62.7)
Median age at second sample collection (min, max)	48.9 (28.0, 76.9)	48.8 (28.1, 76.7)
Median years between first and second sample collection (min, max)	5.0 (2.0, 28.3)	5.0 (1.9, 27.7)
Median years from first sample collection to case diagnosis (min, max)	27.3 (8.8, 38.8)	
Median years from second sample collection to case diagnosis (min, max)	21.2 (5.6, 32.5)	
Case histology		
CLL/SLL	71 (17%)	
DLBCL	76 (18%)	
FL	44 (10%)	
MM	102 (24%)	
MZL	22 (5%)	
Other / NOS	107 (25%)	

Abbreviations: CLL / SLL, chronic lymphocytic leukemia / small lymphocytic lymphoma; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; MM, multiple myeloma; NOS, not otherwise specified.

Table 2.

Associations between serum sCD27 and sCD30 (per natural log increase) from two banked samples and future risk of non-Hodgkin lymphoma and selected subtypes in the Janus Serum Bank.

			First Sample		Second Sample	
Analyte	**Study Group**	**N**	**OR[1] (95% CI)**	**OR[2] (95% CI)**	**OR[1] (95% CI)**	**OR[2] (95% CI)**
sCD27	Control	426	1.0	1.0	1.0	1.0
	All NHL	414	1.1 (0.7-1.8)	0.9 (0.5-1.6)	1.2 (0.8-1.9)	1.1 (0.6-1.8)
	CLL/SLL	70	1.6 (0.7-3.7)	1.7 (0.7-4.7)	**3.0 (1.2-7.5)**	**4.2 (1.5-11.6)**
	DLBCL	74	0.9 (0.4-2.0)	1.0 (0.4-2.7)	1.1 (0.5-2.7)	1.0 (0.4-2.7)
	FL	43	0.5 (0.2-1.6)	0.3 (0.1-1.0)	0.5 (0.2-1.4)	**0.3 (0.1-0.8)**
	MM	102	0.8 (0.4-1.7)	0.7 (0.3-1.6)	0.7 (0.4-1.5)	0.8 (0.3-1.7)
	MZL	22	2.8 (0.6-13.0)	1.9 (0.3-11.2)	**6.9 (1.5-31.1)**	3.8 (0.7-22.3)
	Other/NOS	103	1.6 (0.8-3.4)	1.1 (0.5-2.5)	1.3 (0.6-2.8)	1.1 (0.5-2.5)
			P_{Het} = 0.33	P_{Het} = 0.18	P_{Het} = 0.05	P_{Het} = 0.006
sCD30	Control	384	1.0	1.0	1.0	1.0
	All NHL	376	1.1 (0.8-1.4)	1.1 (0.8-1.4)	1.2 (0.9-1.7)	1.2 (0.8-1.7)
	CLL/SLL	64	0.7 (0.4-1.3)	0.6 (0.3-1.2)	0.8 (0.4-1.5)	0.6 (0.3-1.1)
	DLBCL	66	0.6 (0.3-1.1)	0.6 (0.3-1.1)	1.0 (0.5-1.8)	1.0 (0.4-2.7)
	FL	39	1.7 (1.0-3.1)	**2.3 (1.2-4.4)**	**2.2 (1.1-4.4)**	**2.9 (1.4-4.4)**
	MM	89	0.8 (0.5-1.4)	0.9 (0.5-1.6)	0.8 (0.5-1.4)	0.9 (0.5-1.6)
	MZL	19	1.8 (0.8-4.2)	1.6 (0.6-4.1)	**3.3 (1.3-8.4)**	2.4 (0.9-6.9)
	Other/NOS	99	1.6 (1.0-2.4)	1.6 (1.0-2.5)	1.5 (0.9-2.4)	1.4 (0.8-2.5)
			P_{Het} = 0.007	P_{Het} = 0.004	P_{Het} = 0.09	P_{Het} = 0.01

Abbreviations: OR, odds ratio; CI, confidence interval; NHL, non-Hodgkin lymphoma; CLL / SLL, chronic lymphocytic leukemia / small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MM, multiple myeloma; MZL, marginal zone lymphoma; NOS, not otherwise specified. P_{Het}, *P*-value from test of OR heterogeneity across NHL subtypes.

Note: results in bold-face type are statistically significant ($P < 0.05$).

[1]OR per natural log increase calculated using polytomous regression model adjusting for sex, age at first sample collection, years between first and second sample collection, prior subject inclusion in prior study of persistent organochlorine pollutants.

[2]OR per natural log increase calculated using polytomous regression model simultaneously adjusting for sCD27 and sCD30 along with the aforementioned model covariates.

Table 3.

Associations between difference in sCD27 and sCD30 concentrations across samples and future risk of non-Hodgkin lymphoma in the Janus Serum Bank.

		Difference across samples (sample$_2$ - sample$_1$)				
Analyte	**Study Group**	**Mean Difference (SD)**	**OR[1] (95% CI)**	***P***	**OR[2] (95% CI)**	***P***
sCD27 (U/mL)	Control	8.4 (12.0)	1.0		1.0	
	All NHL	8.5 (11.7)	1.0 (0.9-1.2)	0.88	1.0 (0.9-1.2)	0.79
	CLL/SLL	11.2 (10.8)	1.3 (1.0-1.7)	0.06	**1.4 (1.1-1.9)**	**0.02**
	DLBCL	9.2 (11.7)	1.0 (0.8-1.4)	0.76	0.9 (0.7-1.3)	0.68
	FL	6.9 (9.1)	0.9 (0.7-1.3)	0.61	0.9 (0.6-1.3)	0.42
	MM	6.6 (12.4)	0.9 (0.7-1.1)	0.32	0.9 (0.7-1.2)	0.47
	MZL	14.6 (12.1)	1.5 (1.0-2.3)	0.06	1.4 (0.9-2.4)	0.17
	Other/NOS	7.3 (12.1)	0.9 (0.7-1.1)	0.39	0.9 (0.7-1.2)	0.61
			P_{Het} = 0.15		P_{Het} = 0.08	
sCD30 (ng/mL)	Control	1,305 (22,290)	1.0		1.0	
	All NHL	2,712 (18,311)	1.1 (0.9-1.3)	0.44	1.1 (0.9-1.3)	0.54
	CLL/SLL	2,401 (12,7998)	1.1 (0.8-1.5)	0.70	0.9 (0.7-1.3)	0.58
	DLBCL	5,198 (10,009)	1.3 (0.9-1.8)	0.14	1.4 (0.9-2.0)	0.14
	FL	1,400 (29,849)	1.0 (0.8-1.4)	0.86	1.1 (0.7-1.6)	0.66
	MM	3,141 (10,963)	1.1 (0.8-1.5)	0.55	1.2 (0.8-1.8)	0.39
	MZL	9,443 (35,166)	1.6 (0.9-2.9)	0.09	1.3 (0.7-2.7)	0.42
	Other/NOS	94 (20,248)	0.9 (0.7-1.2)	0.56	1.0 (0.7-1.2)	0.73
			P_{Het} = 0.58		P_{Het} = 0.48	

Abbreviations: OR, odds ratio; CI, confidence interval; NHL, non-Hodgkin lymphoma; CLL / SLL, chronic lymphocytic leukemia / small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MM, multiple myeloma; MZL, marginal zone lymphoma; NOS, not otherwise specified. P_{Het}, *P*-value from test of OR heterogeneity across NHL subtypes.

Note: results in bold-face type are statistically significant ($P < 0.05$).

[1] OR per increase in the difference equivalent to one standard deviation among controls (sCD27, 12.0 U/mL; sCD30, 22,290 ng/mL), calculated using polytomous regression model adjusting for sex, age at first sample collection, years between first and second sample collection, and prior subject inclusion in prior study of persistent organochlorine pollutants.

[2] OR per increase in the difference equivalent to one standard deviation among controls (sCD27, 12.0 U/mL; sCD30, 22,290 ng/mL), calculated using polytomous regression model simultaneously adjusting for sCD27 and sCD30 along with the aforementioned model covariates.

Table 4.

Joint analysis of dichotomized analyte concentrations (≤ vs. > median) across both samples and future risk of non-Hodgkin lymphoma (overall and by subtype) in the Janus Serum Bank

	Dichotomized Analyte Concentration Across Samples (Sample 1 / Sample 2)									
Analyte	**Low[1] / Low (Reference)**	**Low / High[2]**			**High / Low**			**High / High**		
Study Group	**N**	**N**	**OR[3] (95% CI)**	**OR[4] (95% CI)**	**N**	**OR[3] (95% CI)**	**OR[4] (95% CI)**	**N**	**OR[3] (95% CI)**	**OR[4] (95% CI)**
sCD27										
Controls	161	51	-	-	52	-	-	162	-	-
All NHL	149	68	1.5 (1.0-2.3)	1.5 (1.0-2.3)	51	1.1 (0.7-1.7)	1.0 (0.7-1.7)	146	1.0 (0.7-1.4)	1.0 (0.7-1.4)
CLL/SLL	22	9	1.4 (0.6-3.2)	1.5 (0.6-3.4)	6	0.9 (0.3-2.4)	1.0 (0.4-2.7)	33	1.6 (0.9-2.8)	1.7 (0.9-3.2)
DLBCL	27	16	1.9 (0.9-3.9)	1.8 (0.9-3.8)	8	1.0 (0.4-2.4)	1.0 (0.4-2.5)	23	0.9 (0.5-1.7)	1.0 (0.5-1.8)
FL	17	7	1.1 (0.4-3.0)	1.1 (0.4-3.0)	7	1.0 (0.4-2.7)	0.9 (0.3-2.4)	12	0.7(0.3-1.5)	0.5 (0.2-1.2)
MM	39	18	1.5 (0.8-3.0)	1.6 (0.8-3.1)	14	1.0 (0.4-2.1)	1.0 (0.5-2.0)	31	0.8 (0.4-1.3)	0.8 (0.4-1.3)
Other / NOS[5]	40	12	1.3 (0.7-2.5)	1.3 (0.7-2.5)	16	1.2 (0.6-2.3)	1.2 (0.6-2.3)	35	1.1 (0.7-1.8)	1.0 (0.6-1.7)
sCD30										
Controls	133	59	-	-	59	-	-	133	-	-
All NHL	129	57	1.0 (0.7-1.6)	1.0 (0.6-1.5)	53	0.9 (0.6-1.5)	1.0 (0.6-1.6)	137	1.1 (0.8-1.5)	1.1 (0.8-1.6)
CLL/SLL	29	7	0.6 (0.2-1.3)	0.5 (0.2-1.3)	7	0.5 (0.2-1.3)	0.5 (0.2-1.3)	21	0.7 (0.4-1.3)	0.6 (0.3-1.2)
DLBCL	23	14	1.4 (0.7-3.0)	1.3 (0.6-2.7)	9	1.0 (0.4-2.3)	1.0 (0.4-2.4)	20	0.9 (0.5-1.7)	0.9 (0.5-1.8)
FL	10	4	0.9 (0.3-3.0)	0.9 (0.3-3.0)	5	1.1 (0.4-3.6)	1.2 (0.4-3.8)	20	2.1 (1.0-4.8)	**2.5 (1.1-5.9)**
MM	31	13	1.0 (0.5-2.1)	0.9 (0.4-1.9)	17	1.2 (0.6-2.4)	1.4 (0.7-2.7)	28	0.9 (0.5-1.5)	1.0 (0.5-1.7)
Other / NOS[5]	32	15	1.2 (0.7-2.3)	1.2 (0.6-2.3)	11	1.0 (0.5-2.0)	1.0 (0.4-2.4)	41	1.4 (0.8-2.3)	1.4 (0.8-2.3)

Abbreviations: OR, odds ratio; CI, confidence interval; NHL, non-Hodgkin lymphoma; CLL / SLL, chronic lymphocytic leukemia / small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MM, multiple myeloma; NOS, not otherwise specified.

Note: results in bold-face type are statistically significant ($P < 0.05$).

[1] ≤ median concentration among controls.

[2] > median concentration among controls.

[3] OR calculated using polytomous regression model adjusting for sex, age at first sample collection, years between first and second sample collection, and prior subject inclusion in prior study of persistent organochlorine pollutants.

[4] OR calculated using polytomous regression model simultaneously adjusting for sCD27 and sCD30 along with the aforementioned model covariates.

[5] Includes marginal zone lymphoma.