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Circulating immune markers and risks of non-Hodgkin lymphoma subtypes: a pooled analysis

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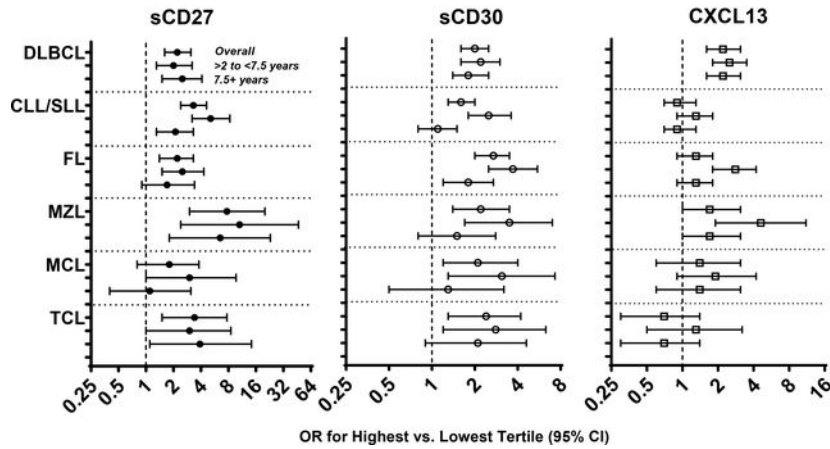
Abstract

Although pre-diagnostic circulating concentrations of the immune activation markers soluble CD27 (sCD27), sCD30 and chemokine ligand-13 (CXCL13) have been associated with non-Hodgkin lymphoma (NHL) risk, studies have been limited by sample size in associations with NHL subtypes. We pooled data from eight nested case-control studies to investigate subtype-specific relationships for these analytes. Using polytomous regression, we calculated odds ratios (ORs) with 95% confidence intervals (CIs) relating study-specific analyte tertiles to selected subtypes vs. controls (n=3,310): chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; n=623), diffuse large B cell lymphoma (DLBCL; n=621), follicular lymphoma (FL; n=398), marginal zone lymphoma (MZL; n=138), mantle cell lymphoma (MCL; n=82) and T cell lymphoma (TCL; n=92). We observed associations with DLBCL for elevated sCD27 [OR for 3rd vs. 1st tertile (OR_{T3})=2.2, 95% CI=1.6–3.1], sCD30 (OR_{T3}=2.0, 95% CI=1.6–2.5) and CXCL13 (OR_{T3}=2.3, 95% CI=1.8–3.0). We also observed associations with sCD27 for CLL/SLL (OR_{T3}=3.3, 95% CI=2.4–4.6), MZL (OR_{T3}=7.7, 95% CI=3.0–20.1) and TCL (OR_{T3}=3.4, 95% CI=1.5–7.7), and between sCD30 and FL (OR_{T3}=2.7, 95% CI=2.0–3.5). In analyses stratified by time from phlebotomy to case diagnosis, the sCD27-TCL and all three

DLBCL associations were equivalent across both follow-up periods (<7.5, ≥7.5 years). For other analyte-subtype comparisons, associations were stronger for the follow-up period closer to phlebotomy, particularly for indolent subtypes. In conclusion, we found robust evidence of an association between these immune markers and DLBCL, consistent with hypotheses that mechanisms related to immune activation are important in its pathogenesis. Our other findings, particularly for the rarer subtypes MZL and TCL, require further investigation.

Graphical Abstract

Associations of individual pre-diagnosis serum immune markers with NHL risk by histologic subtype, overall and stratified by years of follow-up (>2 to <7.5, 7.5+ years) after blood draw

Keywords

immune markers; sCD27; sCD30; CXCL13; non-Hodgkin lymphoma

Introduction

Non-Hodgkin lymphoma (NHL), the seventh most commonly diagnosed cancer in the United States,[1] is a collection of malignancies arising from lymphocytes. Although NHL is not a formal category in the World Health Organization (WHO) classification of lymphoid neoplasms, it is a traditional term that has typically included most types of mature B cell and T/NK cell malignancies as defined by WHO.[2] The most common NHL subtypes, all of B cell origin, include diffuse large B cell lymphoma (DLBCL; approximately 21% of US cases), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; 18%), follicular lymphoma (FL; 10%), marginal zone lymphoma (MZL; 6%) and mantle cell lymphoma (MCL; 3%). T cell lymphomas (TCL) are rare, collectively making up approximately 7% of NHL cases.[3] Many lymphoma subtypes possess distinct genetic characteristics and exhibit markedly different incidence patterns across sex and racial/ethnic groups.[4] Additionally, increasing evidence supports the existence of distinct etiologies

across lymphoid malignancies, including numerous NHL subtype-specific associations with genetic, medical and lifestyle risk factors identified in large consortial studies.[5–13]

Several conditions involving severe immune dysregulation are established risk factors for NHL; examples include human immunodeficiency virus (HIV) and other infectious agents, history of congenital or iatrogenic immunosuppression, and selected autoimmune diseases, although the prevalence of these conditions is low.[8–11, 14] Many of these risk factor associations are subtype-specific (e.g., human T-lymphotropic virus type I with adult T cell leukemia/lymphoma; *Helicobacter pylori* with gastric mucosa-associated lymphoid tissue lymphoma), or more strongly associated with some subtypes than others (e.g., HIV primarily with DLBCL).[9, 14]

Subtle alterations in immune function may also influence NHL risk. Several nested case-control investigations within population-based cohorts have reported associations with NHL risk for pre-diagnostic circulating levels of selected markers of immune activation, especially B cell activation. The markers most consistently associated with NHL include soluble CD27 (sCD27) and sCD30, which are cleaved fragments of the lymphocyte transmembrane proteins CD27 and CD30 measured as markers of immune activation, and chemokine ligand-13 (CXCL13), a B cell chemoattractant to secondary lymphoid tissue.[15–27] Most studies have reported that elevated levels of these three immune markers are associated with increased subsequent risk of NHL, although it is unclear to what extent these associations vary by lymphoma subtype or reflect early disease-induced effects, as has been suggested by some longitudinal studies.[24, 25, 28] The precise time frame that would reflect disease-induced rather than etiologic effects is not known for most subtypes; the known differences in the aggressiveness of pathogenesis between, for example, the aggressive DLBCL subtype and the more indolent subtypes like CLL/SLL, FL or MZL suggest subtype-specific variability in the preclinical stages.[29] Several studies have individually explored associations with common subtypes, although these investigations have typically been limited by sample size.[15, 17–19, 21, 24–27] Rarer subtypes such as MZL, TCL and MCL have been studied infrequently, with often uninformative findings.[24, 26, 27]

To clarify the relationship between circulating levels of sCD27, sCD30, CXCL13 and risk of individual NHL subtypes, both overall and across varying periods of follow-up, we conducted a pooled analysis across eight nested case-control studies that measured at least one of these three markers.

Materials and Methods

Study population

We pooled data from eight nested case-control studies conducted within 11 cohorts of presumed immunocompetent adults: the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO; two studies conducted);[18, 21] the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC);[19] the Women's Health Initiative (WHI);[17] the Shanghai Women's Health Study (SWHS), Shanghai Cohort Study (SCS) and Singapore Chinese Health Study (SCHS);[16] the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS);[26] the Campaign Against Cancer and Stroke (CLUE-I) and Campaign

Against Cancer and Heart Disease (CLUE-II);[25] and the Department of Defense Serum Repository (DoDSR) Study. Details regarding the design of each study are provided in Supplementary Table 1 and the Supplementary Methods. Controls were individually matched to cases at a 1:1 ratio for all studies except the DoDSR project, which employed a 2:1 ratio. Six of the nested case-control studies involved immune marker measurements using a single banked serum or plasma sample per participant; two exceptions were the DoDSR (2 samples per subject) and CLUE-I/-II studies (2 samples). For these two studies we selected the single samples (first or last) that yielded a distribution of follow-up time after blood collection most comparable to that of the other studies (median of 5–11 years for the other studies). For this reason, we chose the earliest collected samples for DoDSR (which yielded a median follow-up time to diagnosis of 7 years, whereas the median was 1 year for the latest collected DoDSR sample) and the latest collected sample in CLUE (which yielded a median follow-up time of 10 years, whereas the median was 20 years for the earliest collected CLUE sample; Supplementary Methods).

In an attempt to include all published nested case-control studies investigating NHL and pre-diagnostic concentrations of these immune markers that were conducted in general population cohorts (e.g., excluding cohorts of subjects with HIV/AIDS), we sought to also include data from studies conducted within the Janus Serum Bank, the Northern Sweden Health study and the European Prospective Investigation into Cancer and Nutrition study.[23, 24, 27] However, this could not be accomplished due to data sharing restrictions related to the European Union General Data Protection Regulation Policy.[30]

It is notable that many of the studies included in our pooled analysis used different assays, and/or the same assays at different points in calendar time, to measure the same immune markers (Supplementary Table 1). Given these differences in assay methods (and, when the same assay was used at different times, potential differences across reagent lots), the absolute concentrations of the measurements differ substantially across studies, as expected (Supplementary Figure 1). Therefore, we decided *a priori* to analyze the immune markers as categorical variables, using study-specific control tertiles as cut-points.

Individuals with missing information on circulating levels of the immune markers (sCD27: 3 cases, 2 controls; sCD30: 6 cases, 5 controls; CXCL13: 33 cases, 30 controls) were excluded from analysis of each marker. In addition, we excluded cases diagnosed 2 years after blood collection (n=300) to reduce some of the potential bias from reverse causation due to tumor-induced changes in circulating marker concentrations before clinical diagnosis.[19, 21, 25] In total, 2,455 NHL cases (including 623 CLL/SLL, 621 DLBCL, 398 FL, 138 MZL, 82 MCL and 92 TCL) and 3,310 controls were included in the statistical analysis.

Statistical analysis

We generated univariate statistics summarizing the characteristics of each study and their distributions of the measured sCD27, sCD30 and CXCL13 concentrations as well as cohort-specific Spearman correlation coefficients between levels of the three markers by case-control status and, among cases, by NHL subtype. We first fit study-specific conditional logistic regression models of the matched case-control sets to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for overall NHL in relation to pre-diagnostic circulating

sCD27, sCD30, and CXCL13 (categorized into tertiles based on the cohort-specific control distributions). For this analysis, we excluded broken matched case-control sets (10 cases, 489 controls), leaving a total of 5,266 participants (cases=2,445, controls=2,821). We then conducted meta-analyses of the study-specific findings with NHL as an endpoint using a random effects model and assessed between-study heterogeneity using Cochrane's Q and I^2 statistics. We also performed meta-analyses restricted to B cell lymphomas (76% of all cases) to assess between-study heterogeneity within that cell type. Influence analyses were performed by repeating meta-analyses for each marker after excluding each cohort one at a time. Potential publication bias was evaluated by determining whether there was asymmetry in the shape of a funnel plot and by the p-value from Egger's test.[31]

We also conducted pooled analyses of the combined data set, which permitted more robust subtype-specific analyses. For the pooled analyses we calculated ORs and 95% CIs relating study-specific tertiles of immune marker levels and all NHL using conditional logistic regression; this was done for the dataset overall as well as by sex, sample type (serum, plasma), and follow-up time from blood collection to diagnosis (using the approximate median number of follow-up years as a cut-point; >2 to <7.5 years, ≥7.5 years). In all models we also evaluated parameters testing for multiplicative interaction between circulating marker and study as a means of assessing between-study heterogeneity.

Within the pooled analyses we computed ORs and 95% CIs relating the study-specific tertiles of immune marker concentrations to risk of specific NHL subtypes (CLL/SLL, DLBCL, FL, MCL, MZL, TCL) by fitting polytomous regression models adjusted for age (<55, 55-<65, ≥65 years), sex, race (white, non-white) and study. The output of the polytomous regression analysis also provided a statistical test of the null hypothesis of equality of the ORs across subtypes. In some models we further adjusted for body mass index (BMI; <25, 25-<30, ≥30 kg/m^2) and smoking (never, former, current) using four studies that provided this information (PLCO1, PLCO2, NHS/HPFS, ATBC; all participants in ATBC were smokers). Polytomous regression analyses were conducted both overall and stratified by case time from blood collection to diagnosis (>2 to <7.5, ≥7.5 years). As sensitivity analyses, we repeated analyses including all three immune markers simultaneously in regression models (ATBC and WHI only) and using conditional logistic regression rather than polytomous regression to analyze subtype-specific associations.

Results

Selected characteristics of the participants in the included studies are summarized in Table 1 and Supplementary Table 1. For most studies, the median age at phlebotomy ranged between 57 and 66 years, although DoDSR study participants were younger (median age 28 years). Most of the nested case-control studies included both sexes (although 92% of DoDSR participants were male); however, the ATBC study consisted only of men, the WHI study included only women, and the NHS/HPFS and SWHS/SCS/SCHS studies comprised participants from female-(NHS, SWHS) and male-(HPFS, SCS) restricted cohorts. For the samples included in the pooled analyses, the median length of follow-up from blood collection to diagnosis ranged from 6 (PLCO1) to 12 (ATBC) years and was 7.7 years overall. Two of the eight studies measured all three markers of interest (ATBC, WHI),

five measured two markers (PLCO1, SWHS/SCS/SCHS, NHS/HPFS, CLUE-I/CLUE-II, DoDSR), and one measured only a single marker (PLCO2). In comparisons of the absolute concentrations of measurements across studies, which were made with different assays and/or at different calendar times, the measured absolute concentrations of sCD27 were considerably higher in WHI compared to other studies, while sCD30 measurements in NHS/HPFS were much lower than all other studies (Supplementary Figure 1). The distributions of the three markers were not notably different by sex, BMI, or smoking (Supplementary Table 2). sCD27, sCD30 and CXCL13 were moderately correlated with one another among controls within each cohort, with Spearman correlation coefficients ranging from 0.27 to 0.51 (Supplementary Table 3), which is similar to previous studies.[32, 33] In the two studies that measured all three markers (ATBC and WHI), sCD27 and sCD30 levels were more strongly correlated with one another than with CXCL13 levels.

In meta-analyses of the study-specific findings, we observed statistically significant associations between increased NHL risk and elevated circulating levels of sCD27 (OR for third vs. first study-specific tertile [OR_{T3}]=3.0, 95% CI=2.4 to 3.8; Figure 1), sCD30 (OR_{T3}=2.2, 95% CI=1.8 to 2.7) and CXCL13 (OR_{T3}=1.9, 95% CI=1.4 to 2.6). We observed substantial between-study heterogeneity in OR magnitudes for CXCL13 (I^2=69%, P=0.01), mainly attributable to a null finding for ATBC, but no significant heterogeneity for sCD27 or sCD30 (I^2=0%, P=0.74 and I^2=33%, P=0.16, respectively). In influence analyses, similar summary ORs were observed for all three markers regardless of which study was omitted from a given analysis (Supplementary Tables 4–6). Egger's tests suggested no evidence of publication bias (sCD27: P=0.18, sCD30: P=0.39, CXCL13: P=0.36).

Our findings for risk of NHL overall from the pooled analyses (Table 2) were similar to those from the meta-analyses for each immune marker, with an OR_{T3} of 3.0 (95% CI=2.4 to 3.8; P_{trend}=2.7×10^{-21}) observed for sCD27, an OR_{T3} of 2.2 (95% CI=1.9 to 2.6; P_{trend}=6.8×10^{-24}) for sCD30 and an OR_{T3} of 2.0 for CXCL13 (95% CI=1.7 to 2.3; P_{trend}=5.4×10^{-16}). These findings were also similar by sample type and by sex (Supplementary Table 7), although the association with CXCL13 was slightly stronger among women (OR_{T3}=2.4, 95% CI=1.9 to 3.1, P_{trend}<0.0001; $P_{interaction}$=0.03). In an analysis mutually adjusting for all three markers, these associations became slightly weaker (Table 3). For each marker, the ORs were stronger for NHL cases diagnosed >2 to <7.5 years after blood collection, although the weaker associations for cases diagnosed ≥7.5 years post-phlebotomy still reached statistical significance (Table 4).

In analyses of NHL subtypes, tests of OR heterogeneity across the selected lymphoid malignancies were statistically significant or of borderline significance (sCD27, P=0.03; CXCL13, P<0.0001; sCD30, P=0.06; Table 2). sCD27 levels were most strongly associated with MZL (OR_{T3}=7.7, 95% CI=3.0 to 20.1; P_{trend}=2.3×10^{-6}), followed by TCL (OR_{T3}=3.4, 95% CI=1.5 to 7.7; P_{trend}=0.003), CLL/SLL (OR_{T3}=3.3, 95% CI=2.4 to 4.6; P_{trend}=1.6×10^{-13}), DLBCL (OR_{T3}=2.2, 95% CI=1.6 to 3.1; P_{trend}=9.3×10^{-6}) and FL (OR_{T3}=2.2, 95% CI=1.4 to 3.3; P_{trend}=1.1×10^{-4}). Statistically significant associations with elevated CXCL13 were observed for MZL (OR_{T3}=2.4, 95% CI=1.5 to 3.9; P_{trend}=1.4×10^{-4}), DLBCL (OR_{T3}=2.3, 95% CI=1.8 to 3.0; P_{trend}=3.9×10^{-12}) and FL (OR_{T3}=1.8, 95% CI=1.4 to 2.4; P_{trend}=2.7×10^{-5}). For sCD30, the OR_{T3} estimates were similar in size across

subtypes (range of OR_{T3}=1.6–2.7, Table 2). Our subtype findings did not change with adjustment for BMI or smoking (Supplementary Table 8); BMI and smoking were not independently associated with three immune markers (Supplementary Table 9). When we modeled the three immune markers simultaneously in the subset of subjects with all three markers measured, sCD27 remained significantly associated with most subtypes (CLL/SLL, DLBCL, MZL and TCL); however, sCD30 was only associated with FL and DLBCL, and CXCL13 with DLBCL (Table 3). When we performed a re-analysis of NHL subtypes using conditional logistic regression models, we observed a similar pattern of associations (Supplementary Table 10).

In analyses stratified by years of follow-up from blood draw to case diagnosis (Table 4), the sCD27-TCL association was comparable across both follow-up periods (OR_{T3}=3.0 and 3.9 for >2 to <7.5 and 7.5 years respectively), as were the DLBCL associations with sCD27 (OR_{T3}=2.0 and 2.5), sCD30 (OR_{T3}=2.2 and 1.8) and CXCL13 (OR_{T3}=2.5 and 2.2). For other analyte-subtype comparisons, we observed stronger associations in the follow-up period closer to diagnosis; this includes the aforementioned sCD27-CLL/SLL, sCD27-MZL and sCD30-FL associations (OR_{T3} weaker by 59%, 38% and 51% respectively comparing 7.5 years post-phlebotomy vs. earlier follow-up period). The subtype-specific associations with all three markers, both overall and across different follow-up periods, were generally consistent after excluding each cohort one at a time (Supplementary Tables 4–6).

Discussion

Our findings from this pooled analysis of 2,455 cases and 3,310 controls from eight nested case-control studies provide strong evidence supporting the existence of etiologic heterogeneity across NHL subtypes in their relationship with pre-diagnostic circulating concentrations of sCD27, sCD30 and CXCL13. We found consistent associations with DLBCL for all three markers, both in individual analyses and when fit simultaneously in a single model. We also observed associations between sCD27 and CLL/SLL, MZL and TCL, as well as between sCD30 and FL, all of which remained after adjustment for other immune markers. The associations with DLBCL and between sCD27 and TCL were comparable across different periods of follow-up from blood collection to case diagnosis, while for other analyte-subtype comparisons (indolent subtypes in particular) the associations were weaker for the follow-up period closer to diagnosis.

This pooled analysis is the largest investigation of pre-diagnostic circulating immune markers and NHL conducted to date and the first to investigate immune marker associations across both common and rarer subtypes overall and across different periods of follow-up. As such, it provides a more complete picture of these relationships than in past individual studies, which had limited statistical power to investigate subtype-specific effects and often excluded rarer subtypes from consideration. A recent meta-analysis of studies investigating serum immune markers and NHL included analyses by histologic subtype.[34] However, due to the reliance on the limited study-specific subtype findings reported in the literature, that meta-analysis only assessed common subtypes (CLL/SLL, DLBCL, FL) and did not consider differences in effects by time from blood collection to subtype diagnosis.

The presence of substantial heterogeneity in study-specific effects further complicates the interpretation of the meta-analysis findings.

The circulating immune markers sCD27, sCD30, and CXCL13, although correlated with one another, are distinct measures of systemic immune activation generated by different biologic processes. Immune activation and in particular a sustained state in which activated B lymphocytes undergo clonal expansion, somatic recombination, and class switching, are hypothesized to increase the potential for unrepaired genetic errors, ultimately leading to B cell lymphomagenesis.[35] sCD27 and sCD30 are the cleaved extracellular fragments of CD27 and CD30, members of the TNF receptor superfamily, and are often found to be elevated in patients with autoimmune disorders and infectious diseases.[36, 37] CD27, expressed on T cells and a subset of B cells, interacts with its ligand CD70 to stimulate T cell proliferation and antibody production in activated B cells.[38] CD30 is preferentially expressed by activated type-2 T cells, which produce cytokines that enhance B cell activation.[38] CXCL13 is a chemokine produced by follicular dendritic and T helper cells that promotes the chemotaxis of antigen-naïve B cells to follicles of secondary lymphoid organs, where B cell activation occurs.[39] Of interest, elevated CXCL13 levels are present in patients with acquired immune deficiency syndrome (AIDS).[40] Further, all three of these markers can be detected in biopsied tissue from some lymphomas. CD27 is expressed by many types of lymphoma, whereas CD30 is mainly detected in classical Hodgkin lymphoma and anaplastic large-cell lymphoma and CXCL13 in FL and some extranodal lymphomas.[41–43]

In our pooled analysis, DLBCL was the NHL subtype most clearly associated with pre-diagnostic levels of these immune markers; all three markers were significantly associated with increased risk of this subtype, both in individual marker analyses and when modeled simultaneously. It is also notable that for each marker, the ORs for DLBCL were comparable in size across different periods of follow-up. DLBCL, the most common NHL subtype in Western countries, is an aggressive B cell malignancy that has been etiologically linked to several conditions involving immune dysregulation.[44] In an analysis of medical and lifestyle factors and risk of individual NHL subtypes conducted by the International Lymphoma Epidemiology Consortium (InterLymph), the largest investigation of its kind to date, the strongest identified risk factors for DLBCL were B cell activating autoimmune diseases and hepatitis C virus (HCV) seropositivity.[9] Studies of organ transplantation recipients and AIDS patients have also consistently reported markedly elevated rates of DLBCL in these populations.[45, 46] Additionally, a genome-wide association study (GWAS) of DLBCL identified genetic susceptibility variants mapping to several gene regions involved in immune recognition and immune function.[6] Collectively, the immunologic conditions and immunoregulatory pathways associated with DLBCL risk (many involving chronic B cell activation) support the plausibility that these biomarkers are capturing subtle, sub-clinical immunologic effects that may also contribute to DLBCL pathogenesis.

The etiologies of CLL/SLL and FL, indolent NHL subtypes commonly diagnosed in Western populations, are poorly understood.[44] A cluster analysis of NHL subtypes within the InterLymph Consortium suggested that risk factors related to immune perturbations (autoimmune diseases, HCV, peptic ulcer as a surrogate for *H. pylori* infection) are of less importance for CLL/SLL and FL compared to other subtypes, including DLBCL,

MZL and peripheral TCLs.[14] GWAS investigations have identified strong associations with FL for variants in the human leukocyte antigen (HLA) Class II gene region, while CLL susceptibility loci have been identified mapping to genes involved in B cell function and immune response (including the HLA region) among other pathways.[13, 47] We found sCD27 and sCD30 to be associated with CLL/SLL and FL, respectively, independent of other markers, although both associations were approximately 50% weaker for cases diagnosed 7.5 years post-phlebotomy than for cases diagnosed closer in time to the date of blood collection. These patterns may suggest a later-stage role in the development of CLL/SLL and FL for the biologic effects captured by these markers. However, given the documented presence of early-disease markers many years prior to CLL and FL diagnosis,[48, 49] it is plausible that reverse causation from prodromal effects of undiagnosed indolent disease affected these findings, given that stronger associations were observed among cases closer to diagnosis. Patterns of immune marker associations compatible with disease-driven effects were previously observed for CLL and FL in a longitudinal analysis involving serial pre-diagnostic samples.[28] In particular, sCD27 is known to be expressed by CLL cells and has been identified as a marker of tumor load.[50]

Our investigation of less common NHL subtypes yielded interesting findings, in particular the strong association of sCD27 with MZL and TCL, including in analyses simultaneously adjusting for all three immune markers. The sCD27 association with TCL was consistent across both follow-up periods, whereas for MZL the association for cases diagnosed 7.5 years after blood collection was 38% weaker than that for cases diagnosed earlier in follow-up, although still strong ($OR_{T3} = 6.5$) and statistically significant. Our finding for sCD27 and MZL, the strongest association observed in our analysis, was also reported in a study nested within the Norwegian Janus Serum Bank that was not included in this pooling project.[24] As there is abundant evidence of markedly elevated relative risks of MZLs in relation to B cell activating autoimmune disorders and selected infectious agents (e.g., *H. pylori* for gastric mucosa-associated lymphoid tissue lymphoma, HCV for splenic and nodal MZL, *Borrelia burgdorferi* for primary cutaneous MZL),[11] it is possible that the strong association between sCD27 and MZL may reflect the importance of a chronic B cell stimulatory state in its etiology. However, as MZLs are also indolent lymphomas, we cannot rule out the possibility that effects from slow-growing tumors account for the elevated sCD27 levels. T cell lymphomas comprise a heterogeneous group of rare genetically and clinically distinct malignancies. The etiology of TCLs remains poorly understood, although selected infectious agents have been linked to specific types (e.g., human T cell lymphotropic virus-1 infection for adult T cell lymphoma / leukemia, Epstein Barr virus for nasal TCL).[44] The InterLymph subtypes analysis observed associations with TCLs for risk factors related to T cell activating autoimmune diseases, most notably for celiac disease and peripheral TCLs.[14] Additionally, eczema was found to be a risk factor for the TCL subgroup of mycosis fungoides/Sezary syndrome tumors.[12, 14] Our findings are consistent with a role for immunologic effects in the development of TCLs, although the underlying biologic mechanisms are unclear.

This pooled analysis has limitations, most notably the substantial (but expected) variation across studies in the measured absolute concentrations of the immune markers. This variation is attributable to differences across studies in the immune marker assays employed,

and potentially also to study differences in specimen types (serum, plasma), processing protocols and storage conditions, and duration of the prospective cohorts involved. We accounted for these differences in our analyses by using study-specific cut-points to define elevated immune marker concentrations. As we observed little between-study heterogeneity in OR estimates, our findings do not appear to have been greatly affected by study differences. The variation across studies in the number of immune markers measured was another limitation, which affected the power of our analyses when simultaneously adjusting for all three markers. Despite the large overall sample size, our project had limited power to detect immune marker associations with the less common subtypes, although we were still able to detect notable findings for MZL and TCL. We did not have information on medical histories of auto-immune diseases and infections known to be associated with both NHL and elevated levels of these immune markers (e.g. Sjögren Syndrome, HIV, HCV) and thus were unable to control for their effects in our analysis. However, given the low prevalence of these conditions in general populations, it is unlikely that they account for the associations observed. Lastly, the use of a single banked sample per subject to assess immune marker concentrations provides limited insight into the long-term variation in concentrations of these analytes, and, in particular, into potential disease-induced changes closer in time to diagnosis. With our large sample size including cohorts with substantial follow-up time, we were able to conduct analyses stratifying on duration of follow-up to assess potential disease bias. However, we were unable to directly assess temporal changes in immune marker concentrations within individuals.

In summary, this pooled analysis of prospective studies investigating circulating sCD27, sCD30 and CXCL13 has identified different patterns of association across NHL subtypes. In particular, we observed clear positive associations with DLBCL for all three markers, consistent with hypotheses that mechanisms related to immune activation are important in the etiology of this malignancy. We also observed positive associations between sCD27 and CLL/SLL, MZL and TCL and between sCD30 and FL, although limitations in sample size and/or differences in these findings across periods of follow-up limit causal inference. Our pooled analysis of previously conducted studies has provided a heretofore unavailable opportunity to investigate subtype-specific relationships with these circulating immune markers. Studies with larger sample sizes are needed to confirm and extend these findings. Additional research is also needed to elucidate the endogenous mechanisms, medical conditions, and exogenous exposures underlying these immune marker associations with NHL subtypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

Data availability statement:

Data analyzed in this study are available from the corresponding author upon request with the permission of the participating cohorts. Please contact the corresponding author for details.

Abbreviations:

ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
CIs	confidence intervals
CLL/SLL	chronic lymphocytic leukemia/small lymphocytic lymphoma
CLUE-I	Campaign Against Cancer and Stroke
CLUE-II	Campaign Against Cancer and Heart Disease
CXCL13	chemokine ligand-13
DLBCL	diffuse large B cell lymphoma
DoDSR	Department of Defense Serum Repository
FL	follicular lymphoma
GWAS	genome-wide association study
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPFS	Health Professionals Follow-up Study
InterLymph	International Lymphoma Epidemiology Consortium
MCL	mantle cell lymphoma
MZL	marginal zone lymphoma
NHL	non-Hodgkin lymphoma
NHS	Nurses' Health Study
ORs	odds ratios
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
sCD27	soluble CD27
sCD30	soluble CD30

SCHS	Singapore Chinese Health Study
SCS	Shanghai Cohort Study
SWHS	Shanghai Women's Health Study
TCL	T cell lymphoma
WHI	Women's Health Initiative

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Novelty and Impact:

This pooled analysis of pre-diagnostic serum immune marker concentrations and non-Hodgkin lymphoma (NHL) subtypes, the first of its kind, provides robust evidence implicating subclinical immune activation effects in the pathogenesis of diffuse large B cell lymphoma, as well as novel insights into the etiologies of rare lymphomas (marginal zone and T cell lymphomas).

(A) sCD27

Study		OR	95% CI	Weight
PLCO1		3.4	[2.0; 5.8]	19.6%
ATBC		2.6	[1.6; 4.2]	24.7%
WHI		3.4	[2.3; 5.1]	35.3%
SWHS/ SCS/SCHS		3.0	[1.6; 5.7]	13.0%
CLUE–I/CLUE–II		1.9	[0.8; 4.6]	7.3%
Random effects model		**3.0**	**[2.4; 3.8]**	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.74$

(B) sCD30

Study		OR	95% CI	Weight
PLCO1		3.4	[2.0; 5.8]	10.3%
ATBC		3.2	[1.9; 5.4]	10.8%
WHI		2.1	[1.5; 3.0]	20.8%
SWHS/ SCS/SCHS		2.9	[1.6; 5.2]	8.9%
NHS/HPFS		1.9	[1.4; 2.6]	23.7%
CLUE–I/CLUE–II		1.3	[0.6; 2.9]	5.3%
DoDSR		1.8	[1.3; 2.6]	20.2%
Random effects model		**2.2**	**[1.8; 2.7]**	**100.0%**

Heterogeneity: $I^2 = 33\%$, $\tau^2 = 0.0153$, $p = 0.17$

(C) CXCL13

Study		OR	95% CI	Weight
PLCO2		2.3	[1.6; 3.5]	19.5%
ATBC		1.1	[0.7; 1.7]	18.7%
WHI		2.8	[1.9; 4.0]	20.1%
NHS/HPFS		2.3	[1.6; 3.2]	21.5%
DoDSR		1.6	[1.1; 2.3]	20.3%
Random effects model		**1.9**	**[1.4; 2.6]**	**100.0%**

Heterogeneity: $I^2 = 69\%$, $\tau^2 = 0.0904$, $p = 0.01$

Figure 1. Forest plots summarizing study-specific conditional logistic models of the association of three immune markers (tertile [T]3 vs. T1) with risk of NHL overall.
CXCL13, chemokine ligand 13; OR, odds ratio; CI, confidence interval; T3: highest tertile, T1: lowest tertile, PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; WHI, Women's Health Initiative; SWHS, Shanghai Women's Health Study, SCS, Shanghai Cohort Study; SCHS, Singapore Chinese Health Study; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; CLUE-1, Campaign Against Cancer and Stroke; CLUE-II, Campaign Against Cancer and Heart Disease; DoDSR, Department of Defense Serum Repository

Analyses of all NHL were conducted using conditional logistic regression models of matched case-control sets (sCD27: 1,208 cases, 1,208 controls, sCD30: 2,138 cases, 2,514 controls, CXCL13: 1,886 cases 2,261 controls)

Table 1.

Summary characteristics of the eight nested case-control studies included in the pooled analysis

Study		N[a]	Age at phlebotomy, years[a] Median (25th, 75th)	Sex, n (%)[a] Men	Women	Race, n (%)[a] White	Non-White	Follow-up time from blood collection to diagnosis, years[a] Median (min, max)	NHL subtype, n (%) CLL/SLL	DLBCL	FL	MCL	MZL	TCL
PLCO1[21]	Control	244	65 (60, 68)	154 (63.1%)	90 (36.9%)	227 (93.0%)	17 (7.0%)							
	Case	244	65 (60, 69)	154 (63.1%)	90 (36.9%)	227 (93.0%)	17 (7.0%)	5.5 (2.0[b], 10.8)	98 (38.9%)	56 (22.2%)	37 (14.7%)	9 (3.6%)	13 (5.2%)	6 (2.4%)
PLCO2[18]	Control	301	63 (60, 67)	191 (63.5%)	110 (36.5%)	293 (97.3%)	8 (2.7%)							
	Case	301	64 (60, 68)	191 (63.5%)	110 (36.5%)	293 (97.3%)	8 (2.7%)	8.0 (5.0, 13.0)	106 (35.2%)	71 (23.6%)	41 (13.6%)	9 (3.0%)	13 (4.3%)	16 (5.3%)
ATBC[19]	Control	271	57 (53, 60)	271 (100.0%)	0 (0.0%)	271 (100.0%)	0 (0.0%)							
	Case	271	57 (53, 61)	271 (100.0%)	0 (0.0%)	271 (100.0%)	0 (0.0%)	11.9 (2.0[b], 23.6)	73 (26.9%)	60 (22.1%)	25 (9.2%)	26 (9.6%)	2 (0.7%)	31 (11.4%)
WHI[17]	Control	433	66 (61, 71)	0 (0.0%)	433 (100.0%)	366 (84.5%)	64 (14.8%)							
	Case	433	66 (61, 70)	0 (0.0%)	433 (100.0%)	394 (91.0%)	38 (8.8%)	6.6 (2.0[b], 15.2)	125 (28.8%)	126 (29.0%)	88 (20.3%)	7 (1.6%)	41 (9.4%)	0 (0.0%)
SWHS/ SCS/ SCHS[16]	Control	184	58 (52, 63)	91 (49.5%)	93 (50.5%)	0 (0.0%)	184 (100.0%)							
	Case	184	58 (51, 63)	91 (49.5%)	93 (50.5%)	0 (0.0%)	184 (100.0%)	9.5 (2.1, 24.4)	13 (7.1%)	15 (8.2%)	4 (2.2%)	1 (0.5%)	0 (0.0%)	13 (7.1%)
NHS/ HPFS[26]	Control	543	61 (54, 66)	220 (40.5%)	323 (59.5%)	472 (86.9%)	71 (13.1							
	Case	543	61 (54, 66)	220 (40.5%)	323 (59.5%)	467 (86.0%)	76 (14.0%)	10.5 (2.1, 22.1)	151 (27.8%)	105 (19.3%)	80 (14.7%)	18 (3.3%)	43 (7.9%)	26 (4.8%)
CLUE-I/ CLUE-II[25]	Control	78	58 (52, 68)	32 (41.0%)	46 (59.0%)	77 (98.7%)	1 (1.3%)							

Study		N[a]	Age at phlebotomy, years[a] Median (25th, 75th)	Sex, n (%)[a]		Race, n (%)[a]		Follow-up time from blood collection to diagnosis, years[a] Median (min, max)	CLL/SLL	DLBCL	FL	MCL	MZL	TCL
				Men	Women	White	Non-White							NHL subtype, n (%)
	Case	78	58 (52, 68)	32 (41.0%)	46 (59.0%)	77 (98.7%)	1 (1.3%)	10.4 (2.4, 24.3)	21 (26.9%)	32 (41.0%)	11 (14.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DoDSR	Control	767	28 (21, 34)	706 (92.0%)	61 (8.0%)	515 (67.1%)	252 (32.9%)							
	Case	391	28 (21, 34)	359 (91.8%)	32 (8.2%)	262 (67.0%)	129 (33.0%)	7.0 (3.0, 19.0)	36 (9.6%)	156 (41.5%)	112 (29.8%)	12 (3.2%)	26 (6.9%)	0 (0.0%)
Total	Control	2821	57 (37, 65)	1665 (59.0%)	1156 (41.0%)	2221 (78.7%)	597 (21.2%)							
	Case	2445	59 (51, 66)	1318 (53.9%)	1127 (46.1%)	1991 (81.4%)	453 (18.5%)	7.7 (2.0[b], 24.4)						

Abbreviations: NHL, non-Hodgkin lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; TCL, T-cell lymphoma; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; WHI, Women's Health Initiative; SWHS, Shanghai Women's Health Study; SCS, Shanghai Cohort Study; SCHS, Singapore Chinese Health Study; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; CLUE-1, Campaign Against Cancer and Stroke; CLUE-II, Campaign Against Cancer and Heart Disease; DoDSR, Department of Defense Serum Repository

[a] Summary characteristics including number of cases and controls are derived from data (n=5,266; case=2,445, control=2,821) excluding broken matched case-control sets (10 cases, 489 controls).

[b] Follow-up time from blood collection to diagnosis is >2.0 years but rounded to the first decimal place.

Table 2.

ORs and 95% CIs for NHL risk, overall and by histologic subtype in the pooled analysis

	All[a]		CLL/SLL[b]		DLBCL[b]		FL[b]		MCL[b]		MZL[b]		TCL[b]		P-value from test of heterogeneity by subtype
	N_cases/N_controls	OR (95% CI)	N_cases	OR (95% CI)	N_cases	OR (95% CI)	N_cases	OR (95% CI)	N_cases	OR (95% CI)	N_cases	OR (95% CI)	N_cases	OR (95% CI)	
sCD27, U/ml															
T1[c]	232/397	1	55	1	56	1	39	1	12	1	5	1	8	1	0.03
T2	363/403	1.7 (1.3, 2.1)	90	1.6 (1.1, 2.3)	100	1.7 (1.2, 2.4)	44	1.1 (0.7, 1.8)	11	0.9 (0.4, 2.1)	14	2.9 (1.0, 8.1)	18	2.3 (1.0, 5.3)	
T3	613/408	3.0 (2.4, 3.8)	185	3.3 (2.4, 4.6)	133	2.2 (1.6, 3.1)	82	2.2 (1.4, 3.3)	20	1.8 (0.8, 3.8)	37	7.7 (3.0, 20.1)	24	3.4 (1.5, 7.7)	
P-trend		2.7×10^{-21}		1.6×10^{-13}		9.3×10^{-6}		1.1×10^{-4}		0.11		2.3×10^{-6}		0.003	
P heterogeneity by study		0.38													
sCD30, ng/ml															
T1	500/845	1	130	1	127	1	72	1	15	1	28	1	17	1	0.06
T2	606/812	1.3 (1.1, 1.6)	155	1.2 (0.9, 1.5)	152	1.2 (0.9, 1.5)	92	1.3 (0.9, 1.8)	25	1.6 (0.9, 3.1)	29	1.0 (0.6, 1.8)	18	1.1 (0.5, 2.1)	
T3	1032/857	2.2 (1.9, 2.6)	232	1.6 (1.3, 2.0)	269	2.0 (1.6, 2.5)	193	2.7 (2.0, 3.5)	33	2.1 (1.2, 4.0)	68	2.2 (1.4, 3.5)	41	2.4 (1.3, 4.2)	
P-trend		6.8×10^{-24}		4.9×10^{-5}		6.5×10^{-10}		1.7×10^{-12}		0.02		1.9×10^{-4}		0.002	
P heterogeneity by study		0.01													
CXCL13, pg/ml															
T1	481/783	1	165	1	104	1	81	1	20	1	24	1	27	1	<.0001
T2	541/717	1.3 (1.1, 1.5)	126	0.7 (0.6, 0.9)	148	1.4 (1.1, 1.8)	105	1.3 (1.0, 1.8)	20	1.0 (0.5, 1.8)	33	1.3 (0.8, 2.3)	21	0.7 (0.4, 1.3)	
T3	864/761	2.0 (1.7, 2.3)	193	1.0 (0.8, 1.3)	260	2.3 (1.8, 3.0)	155	1.8 (1.4, 2.4)	32	1.6 (0.9, 2.8)	66	2.4 (1.5, 3.9)	24	0.9 (0.5, 1.5)	

	All[a]		CLL/SLL[b]		DLBCL[b]		FL[b]		MCL[b]		MZL[b]		TCL[b]		P-value from test of heterogeneity by subtype
	N_cases/ N_controls	OR (95% CI)	N_cases	OR (95% CI)	N_cases	OR (95% CI)	N_cases	OR (95% CI)	N_cases	OR (95% CI)	N_cases	OR (95% CI)	N_cases	OR (95% CI)	
P-trend		5.4×10^{-16}		0.67		3.9×10^{-12}		2.7×10^{-5}		0.09		1.4×10^{-4}		0.57	
P heterogeneity by study		0.67													

Abbreviations: sCD27, soluble CD27; sCD30, soluble CD30; CXCL13, chemokine ligand 13; NHL, non-Hodgkin lymphoma; OR, odds ratio; CI, confidence interval, CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; TCL, T-cell lymphoma; T, tertile

[a] Analyses of all NHL were conducted using conditional logistic regression models of matched case-control sets (sCD27: 1,208 cases, 1,208 controls, sCD30: 2,138 cases 2,514 controls, CXCL13: 1,886 cases 2,261 controls)

[b] Polytomous regression models were adjusted for age (<55, 55–<65, 65), sex, race (white, non-white) and study

[c] Tertile cut-points: sCD27 (PLCO1=51.6, 68.2 U/ml, ATBC=43, 60 U/ml, WHI=192.1, 251.9 U/ml, SWHS/SCS/SCHS=77, 105 U/ml, CLUE-I/CLUE-II=41.5, 54.9 U/ml), sCD30 (PLCO1=10.0, 16.7 ng/ml, ATBC=19.3, 29.0 ng/ml, WHI=26.1, 35.1 ng/ml, SWHS/SCS/SCHS=26.8, 36.3 ng/ml, NHS/HPFS=1.0, 1.3 ng/ml, CLUE-I/CLUE-II=27.4, 36.3 ng/ml, DoDSR=27.1, 38.7 ng/ml), and CXCL13 (PLCO2=13.2, 17.8 pg/ml, ATBC=13.4, 21.5 pg/ml, WHI=46.5, 66.7 pg/ml, NHS/HPFS=30.5, 40.4 pg/ml, DoDSR=37.9, 57.7 pg/ml).

Table 3.

Associations of individual pre-diagnosis serum immune markers with NHL risk by histologic subtype with mutual adjustment for all three markers

	All[a]	CLL/SLL[b]	DLBCL[b]	FL[b]	MCL[b]	MZL[b]	TCL[b]	P-value from test of heterogeneity by subtype
N_{cases} ($N_{controls}$=814[c])	702 ($N_{controls}$=702)	198	186	113	33	43	31	
sCD27, U/ml								0.13
T1[d]	1	1	1	1	1	1	1	
T2	**1.7 (1.2, 2.3)**	**1.6 (1.0, 2.6)**	**1.9 (1.2, 3.1)**	0.9 (0.5, 1.6)	1.0 (0.4, 2.7)	**1.6 (0.5, 5.0)**	**3.6 (1.0, 13.3)**	
T3	**2.3 (1.7, 3.3)**	**2.6 (1.6, 4.1)**	**1.8 (1.1, 3.1)**	1.3 (0.7, 2.3)	1.9 (0.8, 4.9)	**4.2 (1.4, 12.6)**	**4.8 (1.3, 17.8)**	
P-value	9.1×10^{-7}	4.0×10^{-5}	**0.04**	0.31	0.13	**0.003**	**0.02**	
P heterogeneity by study	0.55							
sCD30, ng/ml								0.25
T1	1	1	1	1	1	1	1	
T2	1.3 (0.9, 1.7)	1.2 (0.8, 1.8)	1.1 (0.7, 1.8)	1.0 (0.5, 1.9)	2.2 (0.8, 5.9)	0.8 (0.3, 2.2)	1.3 (0.5, 3.8)	
T3	**1.6 (1.2, 2.3)**	1.4 (0.9, 2.2)	**1.7 (1.1, 2.8)**	**2.6 (1.4, 4.8)**	1.3 (0.4, 3.9)	1.2 (0.4, 3.0)	1.8 (0.6, 5.2)	
P-value	**0.002**	0.17	**0.02**	**0.0003**	0.80	0.67	0.29	
P heterogeneity by study	0.17							
CXCL13, pg/ml								**0.03**
T1	1	1	1	1	1	1	1	
T2	**1.3 (1.0, 1.8)**	0.8 (0.5, 1.2)	1.4 (0.9, 2.2)	**2.0 (1.1, 3.6)**	1.6 (0.7, 3.8)	2.3 (0.8, 6.7)	0.9 (0.4, 2.3)	
T3	**1.3 (1.0, 1.8)**	0.8 (0.5, 1.2)	**1.9 (1.2, 3.0)**	1.5 (0.8, 2.8)	1.1 (0.4, 3.0)	2.4 (0.8, 6.9)	0.7 (0.3, 1.8)	
P-value	0.08	0.29	**0.003**	0.31	0.94	0.14	0.47	
P heterogeneity by study	**0.01**							

Abbreviations: sCD27, soluble CD27; sCD30, soluble CD30; CXCL13, chemokine ligand 13; NHL, non-Hodgkin lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; TCL, T-cell lymphoma; T, tertile.

[a] Analyses of all NHL were conducted using conditional logistic regression models of matched case-control sets (702 cases, 702 controls)

[b] Polytomous regression models were adjusted for age (<55, 55–<65, 65), sex, race (white, non-white) and study

[c] Number of controls used in polytomous regression models

[d] Tertile cut-points: sCD27 (PLCO1=51.6, 68.2 U/ml, ATBC=43, 60 U/ml, WHI=192.1, 251.9 U/ml, SWHS/SCS/SCHS=77, 105 U/ml, CLUE-I/CLUE-II=41.5, 54.9 U/ml), sCD30 (PLCO1=10.0, 16.7 ng/ml, ATBC=19.3, 29.0 ng/ml, WHI=26.1, 35.1 ng/ml, SWHS/SCS/SCHS=26.8, 36.3 ng/ml, NHS/HPFS=1.0, 1.3 ng/ml, CLUE-I/CLUE-II=27.4, 36.3 ng/ml, DoDSR=27.1, 38.7 ng/ml), and CXCL13 (PLCO2=13.2, 17.8 pg/ml, ATBC=13.4, 21.5 pg/ml, WHI=46.5, 66.7 pg/ml, NHS/HPFS=30.5, 40.4 pg/ml, DoDSR=37.9, 57.7 pg/ml).

Table 4.

Associations of individual pre-diagnosis serum immune markers with NHL risk by histologic subtype, stratified by years of follow-up (>2 to <7.5, ≥7.5 years) after blood draw

	All[a]	CLL/SLL[b]	DLBCL[b]	FL[b]	MCL[b]	MZL[b]	TCL[b]	P-value from test of heterogeneity by subtype
sCD27								
>2 to <7.5 years								**0.03**
N_cases (N_controls=1431[c])	637 (N_controls=637)	186	153	104	21	33	26	
OR (95% CI)								
T1[d]	1	1	1	1	1	1	1	
T2	**1.7 (1.2, 2.4)**	**1.9 (1.1, 3.2)**	1.3 (0.8, 2.0)	1.0 (0.6, 1.8)	1.3 (0.3, 4.9)	**5.7 (1.2, 25.9)**	1.6 (0.5, 5.0)	
T3	**5.0 (3.5, 7.1)**	**5.1 (3.2, 8.3)**	**2.0 (1.3, 3.2)**	**2.5 (1.5, 4.3)**	**3.0 (1.0, 9.7)**	**10.6 (2.4, 46.8)**	**3.0 (1.0, 8.5)**	
P-trend	**<2×10^{-16}**	**1.4×10^{-13}**	**8.4×10^{-4}**	**1.2×10^{-4}**	**0.04**	**4.0×10^{-4}**	**0.04**	
P heterogeneity by study	0.44							
7.5 years								0.19
N_cases (N_controls=571)	571 (N_controls=571)	144	136	61	22	23	24	
T1	1	1	1	1	1	1	1	
T2	**1.6 (1.2, 2.2)**	1.4 (0.9, 2.3)	**2.4 (1.4, 3.9)**	1.3 (0.7, 2.6)	0.7 (0.3, 2.2)	1.0 (0.2, 5.2)	3.2 (0.0, 11.8)	
T3	**1.9 (1.4, 2.6)**	**2.1 (1.3, 3.3)**	**2.5 (1.5, 4.1)**	1.7 (0.9, 3.4)	1.1 (0.4, 3.1)	**6.5 (1.8, 23.0)**	**3.9 (1.1, 14.3)**	
P-trend	**1.3×10^{-4}**	**0.001**	**0.001**	0.10	0.81	**0.001**	**0.04**	
P heterogeneity by study	0.47							
sCD30								
>2 to <7.5 years								0.21
N_cases (N_controls=3005[c])	1050 (N_controls=1272)	254	278	193	38	61	38	
T1	1	1	1	1	1	1	1	
T2	**1.4 (1.1, 1.8)**	1.4 (1.0, 2.1)	1.2 (0.8, 1.7)	1.4 (0.9, 2.3)	1.1 (0.4, 3.1)	1.2 (0.5, 2.7)	0.9 (0.3, 2.5)	
T3	**2.9 (2.3, 3.6)**	**2.5 (1.8, 3.6)**	**2.2 (1.6, 3.0)**	**3.7 (2.5, 5.5)**	**3.1 (1.3, 7.3)**	**3.5 (1.7, 7.0)**	**2.8 (1.2, 6.3)**	
P-trend	**<2×10^{-16}**	**5.2×10^{-8}**	**2.4×10^{-7}**	**6.4×10^{-12}**	**0.004**	**1.0×10^{-4}**	**0.006**	

	All[a]	CLL/SLL[b]	DLBCL[b]	FL[b]	MCL[b]	MZL[b]	TCL[b]	P-value from test of heterogeneity by subtype
P heterogeneity by study								
7.5 years								0.16
N_cases (N_controls=3005[c])	1088 (N_controls=1242)	263	270	164	35	64	38	
T1	1	1	1	1	1	1	1	
T2	1.3 (1.0, 1.6)	1.0 (0.7, 1.4)	1.2 (0.8, 1.7)	1.2 (0.8, 1.8)	2.2 (0.9, 5.0)	1.0 (0.5, 1.9)	1.2 (0.5, 3.0)	
T3	**1.7 (1.4, 2.1)**	1.1 (0.8, 1.5)	**1.8 (1.4, 2.5)**	**1.8 (1.2, 2.7)**	1.3 (0.5, 3.2)	1.5 (0.8, 2.8)	2.1 (0.9, 4.6)	
P-trend	**1.3×10^{-6}**	0.43	**6.7×10^{-5}**	**0.002**	0.66	0.15	0.07	
P heterogeneity by study	0.05							
CXCL13								
>2 to <7.5 years								**0.008**
N_cases (N_controls=2664[c])	886 (N_controls=1107)	214	252	175	31	54	29	
T1	1	1	1	1	1	1	1	
T2	**1.4 (1.1, 1.8)**	0.9 (0.6, 1.3)	**1.4 (1.0, 2.1)**	**1.7 (1.1, 2.7)**	0.6 (0.2, 1.7)	**2.6 (1.0, 6.6)**	1.2 (0.5, 3.1)	
T3	**2.3 (1.8, 2.9)**	1.3 (0.9, 1.8)	**2.5 (1.8, 3.5)**	**2.8 (1.8, 4.2)**	1.9 (0.8, 4.2)	**4.6 (1.9, 11.1)**	1.3 (0.5, 3.2)	
P-trend	**3.1×10^{-11}**	0.14	**3.0×10^{-8}**	**8.0×10^{-7}**	0.10	**2.5×10^{-4}**	0.63	
P heterogeneity by study	0.78							
7.5 years								**0.001**
N_cases (N_controls=2664[c])	1000 (N_controls=1154)	270	260	166	41	69	43	
T1	1	1	1	1	1	1	1	
T2	1.2 (0.9, 1.5)	0.7 (0.5, 0.9)	**1.4 (1.0, 2.0)**	1.0 (0.7, 1.6)	1.3 (0.6, 3.0)	0.9 (0.5 1.8)	0.6 (0.3, 1.2)	
T3	**1.7 (1.4, 2.2)**	0.9 (0.7, 1.3)	**2.2 (1.6, 3.1)**	**1.3 (0.9, 1.8)**	1.4 (0.6, 3.1)	**1.7 (1.0, 3.1)**	0.7 (0.3, 1.4)	
P-trend	**1.2×10^{-6}**	0.68	**1.8×10^{-6}**	0.24	0.41	0.05	0.29	
P heterogeneity by study	0.61							

Abbreviations: sCD27, soluble CD27; sCD30, soluble CD30; CXCL13, chemokine ligand 13; T, tertile; NHL, non-Hodgkin lymphoma; OR, odds ratio; CI, confidence interval, CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; TCL, T-cell lymphoma.

[a]Analyses of all NHL were conducted using conditional logistic regression models of matched case-control sets (sCD27: 1,208 cases, 1,208 controls, sCD30: 2,138 cases 2,514 controls, CXCL13: 1,886 cases 2,261 controls)

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[b] Polytomous regression models were adjusted for age (<55, 55–<65, 65), sex, race (white, non-white) and study

[c] Number of controls used in polytomous regression models

[d] Tertile cut-points: sCD27 (PLCO1=51.6, 68.2 U/ml, ATBC=43, 60 U/ml, WHI=192.1, 251.9 U/ml, SWHS/SCS/SCHS=77, 105 U/ml, CLUE-I/CLUE-II=41.5, 54.9 U/ml), sCD30 (PLCO1=10.0, 16.7 ng/ml, ATBC=19.3, 29.0 ng/ml, WHI=26.1, 35.1 ng/ml, SWHS/SCS/SCHS=26.8, 36.3 ng/ml, NHS/HPFS=1.0, 1.3 ng/ml, CLUE-I/CLUE-II=27.4, 36.3 ng/ml, DoDSR=27.1, 38.7 ng/ml), and CXCL13 (PLCO2=13.2, 17.8 pg/ml, ATBC=13.4, 21.5 pg/ml, WHI=46.5, 66.7 pg/ml, NHS/HPFS=30.5, 40.4 pg/ml, NHS/HPFS=37.9, 57.7 pg/ml).