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Non-Hodgkin Lymphoma and circulating markers of inflammation and adiposity in a nested case-control study: The Multiethnic Cohort

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Abstract

Objective—Since immune dysfunction is thought to underlie the development of Non-Hodgkin Lymphoma (NHL), obesity and chronic inflammation may be involved in its etiology. We examined the association of pre-diagnostic inflammatory markers and adipokines with NHL risk.

Methods—We conducted a nested case-control analysis (272 cases and 541 matched controls) within the Multiethnic Cohort. Luminex technology was used to measure a 10-plex panel of cytokines, ELISA assays for adipokines, and an autoanalyzer for C-reactive protein (CRP). Odds ratios (ORs) and 95% confidence intervals (CIs) for tertiles of analytes were estimated by conditional logistic regression.

Results—After a median time of 2.7 years from phlebotomy to diagnosis, interleukin (IL)-10 was significantly related to NHL risk ($OR_{T3\ vs\ T1}$=3.07; 95%CI: 2.02–4.66; p_{trend} <0.001). TNF-α and IL-8 showed borderline elevated risks, while IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, and CRP were not associated with NHL. Leptin but not adiponectin was related to NHL risk ($OR_{T3\ vs\ T1}$=0.48, 95%CI: 0.30–0.76; p_{trend}<0.001). Adjustment for body mass index did not substantially affect the risk estimates. Stratification by subtype indicated significant associations with IL-10 and leptin for follicular but not for diffuse large B-cell lymphoma. Excluding cases diagnosed <1 year after phlebotomy attenuated all associations.

Conclusions—IL-10 was the only cytokine and leptin the only adipokine associated with NHL, but, due to the short follow-up time, pre-clinical effects cannot be excluded.

Impact—Although markers of inflammation and adiposity may provide new insights into the etiology of NHL, they need to be assessed many years before clinical diagnosis.

Keywords

Non-Hodgkin Lymphoma; inflammatory markers; adiponectin; leptin; nested case-control study; prospective cohort; ethnicity

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Introduction

Non-Hodgkin lymphoma (NHL) is an etiologically, clinically, and histologically heterogeneous group of malignant diseases of the lymphocytes (1). Although the etiology of NHL remains unclear, subclinical immune dysfunction is the most consistent risk factor (2–5) and dysregulation of cytokines may mediate disease progression (6). Cytokines regulate lymphocyte development and differentiation; imbalance in the expression of cytokines from T helper 1 (Th1) and Th2 lymphocytes may play an important role in the pathogenesis of NHL (7, 8). Specifically, Th1 cytokines, e.g., tumor necrosis factor (TNF)-α, interleukin (IL)-2, interferon (IFN)-γ, may promote cell-mediated immune response, while Th2 cytokines, e.g., Il-4, IL-5, IL-6, IL1-β, and IL-13, may be involved in the humoral immune response and favor B-cell activation (9). Independent of pathways required for Th1 and Th2 cell development, regulatory T cells (T_{reg}) and IL-17-secreting Th cells (Th17) also play a critical role in autoimmunity (10, 11). As Th17 and T_{reg} cells constitute two opposing immune responses that are critically involved in the modulation of inflammation, a lack of Th17 cells present in the tumor microenvironment of NHL and an imbalance between the two cell types may contribute to NHL etiology (12). Genetic polymorphisms in several cytokine genes, i.e., TNF, IL-4, IL-5, IL-6, IL-10, have been associated with susceptibility to NHL (13–19). However, only a few prospective studies have evaluated pre-diagnostic cytokines and subsequent NHL risk in immunocompetent populations (20–22). These studies observed positive associations for IL-10 (20) and TNF-α (20, 21) and inverse associations for IL-2 (22), IL-5 (21, 22), and IFN-γ (22).

Obesity results in a pathological state of chronic low-level inflammation and altered immune responses that may influence B- and T-lymphocyte function (23) and, thus, the development of NHL. However, the results for obesity and NHL in epidemiologic studies are inconsistent. In one meta-analysis with 10 cohorts and 6 case-control studies, overweight individuals had a 7% greater and obese individuals a 20% greater risk of NHL than normal weight individuals (24), but a pooled analysis of 10,000 cases and 16,000 controls across 18 case-control studies detected only a small excess risk for diffuse large B-cell lymphoma (DLBCL) (25). A recent meta-analysis of 16 prospective studies (26) reported a 7% higher risk for each 5 kg/m^2 increase in BMI but only for DLBLC and not for other subtypes.

Adipocyte-derived adipokines may act as mediators in the NHL pathogenesis. Leptin participates in the inflammation response and enhances B-cell survival (27, 28). Adiponectin attenuates the production of pro-inflammatory cytokines, e.g., TNF-α in human macrophages (29), and increases immunosuppressive cytokines, such as IL-10, in human leukocytes (30). TNF-α may also have an anti-apoptotic effect on B-cells by promoting the activation of transcription factor nuclear factor-κB (31). Genetic polymorphisms in the TNF gene modified the association between body mass index (BMI) and risk for follicular lymphoma (FL) in one study (14), whereas only the risk for DLBCL and not for FL was elevated in obese individuals with specific genotypes of TNF-α or IL-10 supporting the hypothesis that an obesity-related chronic inflammatory response may play a role in the etiology of NHL and DLBCL (32). This case-control study nested within the Multiethnic Cohort (MEC) study explored the relation of pre-diagnostic serum levels of Th1/Th2 cytokines, leptin, adiponectin, and CRP with NHL risk. We hypothesized an elevated NHL risk with Th2, B-cell stimulating, and proinflammatory cytokines (IL-1β, IL-4, IL-5, IL-6, IL-10, TNF-α) and the chemokine IL-8, as well as with leptin, CRP, and protective effects for Th1 cytokines (IFN-γ, IL-2) and adiponectin.

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Materials and Methods

Study population

The MEC is a longitudinal study designed to investigate the association of dietary, lifestyle, and genetic factors with the incidence of cancer. The cohort was assembled in Hawaii and Los Angeles in 1993–1996; details on recruitment and baseline information have been reported previously (33). Briefly, subjects from 5 ethnic groups (African American, Native Hawaiian, Japanese American, Latino, and white) were identified primarily through drivers' license files supplemented with other sources and recruited by mailing a self-administered, 26-page questionnaire on diet, anthropometric measures, medical history, family history of cancer, and lifestyle. A total of 215,251 men and women aged 45 to 75 years were included at baseline and formed a group broadly representative of the general population as verified by a comparison of the cohort's distributions across educational levels and marital status with corresponding census data (33). The study protocol was approved by the Institutional Review Boards of the University of Hawaii and the University of Southern California.

Specimen collection

The prospective MEC biospecimen subcohort was predominately established between 2001 and 2006 by asking surviving cohort members to provide specimens of blood and urine (34). In total, 67,594 cohort members contributed to the biorepository from which the cases and the controls were selected. When comparing the characteristics of repository are broadly representative of all cohort members (Table 1). The median processing times for blood samples was <6 hours and similar for cases and controls.

Selection of cases and controls

Incident cancer cases within the MEC were identified by routine linkages to the Hawaii Tumor Registry, the Los Angeles County Cancer Surveillance Program, and the State of California Cancer Registry, which are part of the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program. Only cases with a date of blood draw before diagnosis were included in the present study. NHL cases were categorized into common subtypes using the classification of lymphoid neoplasms recommended for epidemiologic research based on the International Classification of Diseases for Oncology, Third Edition coding (1). The common subtypes included DLBCL, small lymphocytic lymphoma or chronic lymphocytic leukemia (SLL/CLL), follicular lymphoma (FL), T-cell lymphoma (all types), and all other NHL subtypes. Controls were identified from the biospecimen subcohort who were alive and free of NHL at the age of the case's diagnosis and matched on sex, birth date (within ±1 year), ethnicity (white, Japanese American, Latino, African American, or Native Hawaiian), location (California or Hawaii), date of blood draw (within ±1 year), time of day of blood draw, and fasting hours prior to blood draw (0–<6, 6–<8, 8–<10, or ≥10). The last two matching criteria were needed for analytes other than inflammatory markers. Through linkages with the state death certificate files in California and Hawaii and the National Death Index, we confirmed that the controls were alive at the date of diagnosis of their matched cases.

Lab Assays

Although 275 cases were selected for this analysis, 3 cases had missing serum values and another 3 cases had only 1 control value available resulting in a sample size of 272 cases and 541 controls. All plasma specimens from cases and controls were exposed to the same number of freeze-thaw cycles. The Luminex panel included 8 cytokines (IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, and TNF-α) and one chemokine (IL-8), which were measured using a modification of an Invitrogen (Carlsbad, CA) magnetic high sensitivity 10-plex

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assay kit (LHC0001) and Luminex 200 plate reader. We used 25 μL of serum and 75 μL of diluent buffer per well and decreased the quantity of beads by 25% from manufacturer directions in order to increase sensitivity and reduce clogging of the Luminex plate reader. Each plate held duplicate samples for its assigned subjects. A standard curve was generated using 25 μL per well for each serial dilution of the standard mix provided by the manufacturer. The buffer blank provided by the manufacturer was found to be unacceptable because many samples had lower fluorescence than the blank. Therefore, the lowest fluorescing serum value in each batch was used as a serum blank and subtracted from all samples. Since the fluorescence of many plasma samples was close to 0, using the lowest plasma sample in each batch gave a more reasonable zero value to obtain a relative comparison and non-negative values without significant deviation between batches. Only for IL-8 and Il-10, the buffer blank gave a low value and was used in the calculation as a blank. Values were calculated manually from the fluorescent values reported by the Luminex reader using a standard curve for each analyte plotted on a linear scale and adjusted for % recovery of each analyte determined from spiked serum samples. Extrapolation between 0 and the lower limit of detection (LLOD) was required for <10% of all samples; the rate was higher only for TNF-α and IFN-γ. From previous work with the same assay at our center, we had determined that the extrapolated values gave higher intraclass correlation coefficients than other options, i.e., setting all to 0, setting all values between 0 and LLOD to 1/2 of LLOD, and imputation of new values between 0 and LLOD using the observed distribution ignoring correlation structure between duplicates. Based on these results, we decided that using the extrapolated results between 0 and the LLODs gave more robust results than advertised by the manufacturer.

Leptin and adiponectin were measured utilizing human Leptin (Catalogue #DLP00) and Adiponectin (Catalogue #DRP300) immunoassay kits purchased from R&D Systems, (Minneapolis, MN) according to the manufacturer's directions with detection on a Molecular Devices Versamax tunable microplate reader with Softmax Pro analysis software (Molecular Devices Corp., Sunnyvale, CA) using a 5-parameter analysis of the resulting standard curve. CRP was assessed using a Cobas MiraPlus clinical chemistry analyzer.

The LLODs were as follows: 0.1 pg/mL for IL-1β; 0.2 pg/mL for IL-2, IL-4, IL-5, IL-6, and IL-10; 0.5 pg/mL for IL-8; 0.6 pg/mL for IFN-γ; 1.0 pg/mL for TNF-α; 1.6 ng/mL for leptin; 0.4 μg/mL for adiponectin; and 0.1 mg/L for CRP. Replicate samples of pooled serum were included in each analysis batch for each analyte for quality control. Based on 27 duplicate and 9 triplet samples, the respective within- and between-batch coefficients of variation based on log-transformed marker values were as follows: adiponectin (2.5 and 11.2%); leptin (3.4 and 4.6%); IFN-γ (15.0 and 21.6%); IL-1β (20.9 and 40.7%); IL-2 (10.3 and 16.2%); IL-4 (9.2 and 10.0%); IL-5 (7.1 and 31.1%); IL-6 (8.9 and 18.9%); IL-8 (3.8 and 10.9%); IL-10 (7.8 and 32.1%); TNF-α (10.0 and 43.2%); and CRP (3.5 and 3.2%).

Statistical analysis

SAS version 9.2 (SAS Institute, Inc., Cary, NC) was used to perform all statistical analyses, with a two-sided p value of <0.05 considered statistically significant. Cases and controls were compared using the χ^2 test for categorical variables and the t-test or Wilcoxon rank sum test for continuous variables. Spearman correlation coefficients were used to determine the relation between BMI and analytes. Principal components analysis was used to address the correlation among the cytokines and to create a composite score. The number of components retained for orthogonal rotation was based primarily on functional characteristics of cytokines, e.g., B-cell simulating, pro-inflammatory, with the requirement of an eigenvalue >1.0 and explained variance >60% (35). A factor was constructed as a linear composite of the cytokines with meaningful loading scores, e.g., ≥0.30, and used to calculate a score for each subject.

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Using conditional logistic regression, odds ratios (OR) and 95% confidence intervals (95% CI) were estimated for tertiles of circulating markers and NHL risk. The tertiles were based on the exposure distribution of both cases and controls to ensure a sufficient number of cases and controls within strata. Linear trends were tested by modeling log-transformed continuous variables. Potential confounders, such as years of education, alcohol consumption, cigarette smoking, physical activity, history of blood transfusion, history of asthma, antihistamine, aspirin or acetaminophen use, and dietary intake of fiber, fruit, or vegetables, were examined, but were not included in the final models, as they were not found alone, or in combination, to change the risk estimates by more than 10% (36). For analytes associated with BMI, we repeated all models with and without adjustment for BMI. Sensitivity analyses to control for early disease effects were performed by excluding cases diagnosed <1 year after the blood draw. Heterogeneity of the risk estimates by ethnicity, sex, BMI (<25 vs. ≥ 25 kg/m^2), and years between blood draw and NHL diagnosis (<2.7 vs. ≥ 2.7 years) was tested by a Wald test of cross-product terms. We also evaluated heterogeneity by common NHL subtype (DLBCL, SLL/CLL, and FL) by a Wald test of the parameter estimates obtained from unconditional polytomous logistic regression accounting for the matching factors and performed stratified analyses for DLBCL and FL.

Results

The incident NHL cases were primarily of B-cell origin, with 79 (29%) DLBCL, 51 (19%) SLL/CLL, 49 (18%) FL, 15 (6%) T-cell lymphoma, and 78 (28%) other NHL subtypes. Cases were aged 70.0±7.4 years at blood draw (Table 1), with a median of 2.7 (Interquartile Range 1.4–4.4; range 0.01–11.5) years between blood draw and diagnosis. Whites (27%) and Japanese Americans (27%) comprised the largest ethnic groups, followed by Latinos (23%), African Americans (17%), and Native Hawaiians (6%). Educational level, BMI, and alcohol consumption did not differ between cases and controls. Cases were more likely to be ever smokers (p=0.08) and to have a self-reported history of diabetes (p<0.001) compared to controls (Table 1). They also had statistically significantly lower pre-diagnostic serum levels of leptin (p<0.01) and higher levels of IL-10 (p<0.001) and marginally higher levels of IL-8 (p=0.10) than controls, whereas other markers did not differ by case status. Among controls, BMI was positively correlated with leptin (r=0.45, p<0.0001), CRP (r=0.29, p<0.0001), and IL-6 (r=0.08, p=0.05) and negatively correlated with adiponectin (r=−0.20, p<0.0001), IL-1β (r=−0.09, p=0.03), and TNF-α (r=−0.09, p=0.03).

Only pre-diagnostic serum leptin and IL-10 levels were significantly associated with NHL risk (Table 2). When comparing the highest vs. the lowest tertiles of leptin, NHL risk was reduced by 52% ($OR_{T3\ vs.\ T1}$=0.48 [0.30–0.76]; p_{trend}<0.001), whereas a 3-fold elevation in NHL risk was observed for IL-10 ($OR_{T3\ vs.\ T1}$=3.07 [2.02–4.66]; p_{trend}<0.001). Excluding cases diagnosed <1 year after the blood draw attenuated the risk estimates for leptin ($OR_{T3\ vs.\ T1}$=0.61 [0.37–1.02]; p_{trend}=0.05) and IL-10 ($OR_{T3\ vs.\ T1}$=2.20 [1.38–3.51]; p_{trend}=0.06). The overall associations with TNF-α (P_{trend}= 0.05) and IL-8 (P_{trend}= 0.08) were borderline significant, and none of the remaining markers or the summary measure were associated with NHL risk.

Adjustment for BMI had a limited effect. The inverse association between leptin and NHL risk was slightly strengthened ($OR_{T3\ vs.\ T1}$=0.30 [0.18–0.52]; p_{trend}<0.0001) and the positive association between IL-10 and NHL risk remained significant ($OR_{T3\ vs.\ T1}$=3.09 [2.03–4.70]; p_{trend}<0.001). BMI significantly modified the association of leptin with NHL ($p_{interaction}$<0.0001) but not of IL-10 ($p_{interaction}$ =0.14) although the association was stronger in overweight than normal weight women (Table 3). There was no substantial evidence of effect modification by sex for leptin, IL-10, or IL-8 ($p_{interaction}$>0.23 for all). A weak interaction with ethnicity was seen only for IL-10 ($p_{interaction}$=0.11); the association

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was more pronounced in Latinos ($OR_{T3\ vs.\ T1}$= 4.50 [1.64, 12.38]; p_{trend}<0.01) and whites ($OR_{T3\ vs.\ T1}$= 6.74 [2.75, 16.54]; p_{trend}<0.01) than in the other groups (data not shown).

Pre-diagnostic IL-10 or leptin levels were stronger predictors of NHL risk when the blood collection occurred closer to diagnosis (Table 4); however, a significant interaction with follow-up time was seen only for leptin ($p_{interaction}$<0.0001). For the 51 cases diagnosed >5 years after the blood draw, the estimated risk for the highest tertile of leptin was ($OR_{T3\ vs.\ T1}$=1.46 [0.48–4.45]; p_{trend}=0.80).

Although heterogeneity by NHL subtype was not statistically significant across markers, stratified analyses were performed for DLBCL and FL (Table 5). No significant associations were seen for DLBCL. However, just as in the overall analyses, leptin predicted a lower risk and IL-10 a higher risk for FL. In addition, IL-6 was associated with an elevated risk for FL. The exclusion of cases diagnosed <1 year after blood draw attenuated all risk estimates.

Discussion

In this ethnically diverse nested case-control study, the highest tertile of pre-diagnostic, serum IL-10 levels was associated with a 3-fold elevation in NHL risk, while leptin was associated with a 50% reduction in NHL risk. Given the short follow-up and the attenuated risk estimates after exclusion of cases diagnosed <1 year after blood draw, these associations could be due to pre-clinical effects of the disease. Adjustment for BMI had little effect, but after stratification by NHL subtype, significant associations were restricted to FL. None of the other cytokines, CRP, and adiponectin showed a significant association with NHL risk.

The positive association with IL-10 agrees with one of the three published reports to date (20–22). In contrast to null reports from the New York University Women's Health Study with 92 cases and 184 controls (21) and the Italian component of the European Prospective Investigation into Cancer and Nutrition (EPIC) study with 86 cases and controls each (22), a nested case-control study within the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (297 cases and 297 matched controls) (20) observed a 2-fold higher NHL risk for the top versus the bottom quartile of circulating IL-10 (>7.77 vs. ≤1.93 pg/ml). Consistent with our findings in Table 4 and our results after excluding cases during the first year, the association was attenuated for cases diagnosed 2–5 years after the blood draw and not significant for cases diagnosed 6–10 years post-collection suggesting early tumor-induced effects. None of the three previous analyses reported separate risk estimates for DLBCL and FL (20–22).

On the other hand, two of the previous studies found a positive association with TNF-α (20, 21) and one found an inverse relation (22), whereas the current study found a borderline significant *p*-value for trend that disappeared after excluding cases diagnosed within 1 year of the blood draw. In the PLCO study (20), the highest versus the lowest quartile for circulating TNF-α (>7.98 vs. ≤3.96 pg/ml) levels was associated with a 2-fold higher risk and in the New York University Women's Health Study, higher TNF-α and lower IL-5 levels were marginally associated with the risk for B-cell lymphoma (21). The Italian EPIC study (22) reported a 50% lower risk for higher TNF-α, but the 95% CI included one (p_{trend}=0.10). The inverse association between TNF-α and NHL only reached statistical significance when the analysis was restricted to B-cell lymphomas. The significant inverse associations of IL-2 and IFN-γ with NHL risk in overall models and after excluding cases diagnosed within 2 years of blood donation in the EPIC study (22) also disagree with the null findings observed in the current study.

The role of IL-10 in NHL pathogenesis is unclear. This pleiotropic cytokine with immunosuppressive and anti-inflammatory effects, as well as immunostimulatory effects on

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B-cells (37), may promote lymphomagenesis through the proliferation of B-cells and, thereby increase the likelihood of DNA-modifications, such as chromosomal translocations and oncogene mutations (38). *In vivo* studies of IL-10 knockout mice demonstrated the requirement for IL-10 in the progression of B-cell lymphoma (39). Elevated IL-10 levels have also been observed in NHL cases with poor prognosis (40–42) and in relation to the development of AIDS-related B-cell lymphoma (43). The association of pre-diagnostic serum IL-10 with NHL risk in the current study was observed with a relatively short lag-time between blood donation and diagnosis of 2.7 years. Therefore, reverse causation due to early tumor changes cannot be excluded given that malignant NHL cells produce IL-10 (44, 45).

To our knowledge, this was the first study to prospectively examine the association between circulating leptin and adiponectin levels and subsequent NHL risk. The strong inverse association between leptin and NHL risk observed in the present study appears to be inconsistent with the *a priori* hypothesis that leptin may mediate the positive obesity-NHL association (46). Moreover, the NHL risk estimates for increasing tertile levels of leptin were more pronounced after adjustment for BMI but did not differ substantially by BMI category (<25 vs. ≥ 25 kg/m^2). Leptin is predominately produced by adipose tissue in proportion to body fat mass (47) and plays a central role in regulating energetic homeostasis (48). Recently, data from animal models and human studies have demonstrated the role of leptin in immune homeostasis and the innate and adaptive immune response, as reviewed elsewhere (27, 49). The leptin signaling receptor, OB-Rb, is found on various immune cells, e.g., monocytes, macrophages, NK cells, B-cells, T-cells, regulatory T-cells (49), and genetic polymorphisms in the leptin gene and its receptor support a role for leptin in NHL etiology (19, 46). However, the inverse relation between leptin and NHL risk is difficult to explain and the lack of a biological explanation suggests caution in the interpretation. Through its immunomodulatory effect, leptin may enhance the immune response, resulting in a more effective immunosurveillance by promoting NK-cell cytotoxicity and a switch to Th1-cell immune response (27). In regard to adiponectin, although the present study observed no association between adiponectin levels and NHL risk, adiponectin was higher in newly diagnosed NHL patients (n=28) than in age- and sex-matched controls (n=17) in a small observational study (41). Considering the current clinical and observational data supporting the role of adiponectin in cancer development and prognosis (50), including adiponectin receptor expression in NHL tissue samples (51) and in human lymphocytes (52), further studies are needed to investigate the potential role of adiponectin in NHL pathogenesis.

This study had several strengths including the prospective design that allowed for the pre-diagnostic assessment of biomarkers, the ethnic diversity of the study sample, the population-based sampling frame allowing for generalizability of results, and the principal components analysis that made use of multiple inflammatory marker measures. Although NHL diagnoses could not be confirmed by a re-review of pathology records, the majority of histologic subtypes are expected to be correctly classified within the SEER registry; all cases were diagnosed after the International Classification of Diseases for Oncology, Third Edition, had been adopted (1). The standardized blood collection and processing procedures minimized systematic error and variation in serum marker concentrations; all assays were performed in duplicate.

There are also a number of limitations. The main ones are the availability of a single blood sample for the analysis and the short time period between blood donation and NHL diagnosis (median 2.7 years). Therefore, the results from this study could be the result of reverse causation, i.e., the higher IL-10 and the lower leptin levels may indicate early changes due to lymphoma development as indicated by the lower risk estimates after the

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exclusion of early cases. Longer follow-up of the MEC and other cohorts is needed to confirm these findings. Although information on HIV status, family history of lymphoma, presence of autoimmune disease, immunosuppression, or agricultural exposure was not available and could not be examined as potential confounders, these conditions are expected to be rare in this relatively healthy cohort population. In addition, although the overall number of cases was larger than in previous reports, we had limited ability to detect statistically significant associations in subgroup analyses (20–22).

In conclusion, our findings provide little support for the hypothesis that pre-diagnostic levels of circulating immune markers play a role in the development of NHL. The associations of IL-10 and leptin with NHL risk should be interpreted with caution due to the potential for reverse causation and a lack of a clear biological mechanism. Additional prospective studies with repeated measures over a longer pre-diagnostic time period are needed to provide insight into the etiologic role of subclinical variations in immune markers in NHL pathogenesis.

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Table 1

Characteristics of participants in the Non-Hodgkin Lymphoma nested case-control study within the Multiethnic Cohort (MEC)

Characteristics	Cases[a]	Controls[a]	*p*-value[b]	*MEC*[c]
N	272	541		203,621
Age at blood draw, *y*[d]	70.0 ± 7.4	70.0 ± 7.5		
Fasting prior to blood draw, *hrs* [d]	12.0 ± 4.0	12.3 ± 4.1		
Male[d]	157 (58)	313 (58)		91,905 (45)
Ethnicity[d]				
White	74 (27)	148 (27)		49,604 (24)
Japanese American	72 (27)	143 (27)		57,011 (28)
Latino	62 (23)	123 (23)		47,516 (24)
African American	47 (17)	94 (17)		34,971 (17)
Native Hawaiian	17 (6)	33 (6)		14,519 (7)
BMI, kg/m^2	27.0 ± 5.4	26.4 ± 4.4	0.11	26.1±5.1
Overweight (25.0–29.9 kg/m^2)	106 (39)	219 (40)		72,739 (36)
Obese (≥30.0 kg/m^2)	57 (21)	96 (18)		34,515 (17)
Secondary or higher education	182 (67)	345 (64)	0.39	110, 471 (55)
Alcohol intake ≥1 drink/month	137 (50)	284 (53)	0.57	114,129 (56)
Ever smoker	164 (60)	291 (54)	0.08	112,185 (55)
Pack-years of cigarette smoking	10.4 ±15.1	9.8 ± 15.2	0.55	10.1±15.0
Diabetes, self-reported	36 (13)	22 (4)	**<0.001**	24,342 (12)
Circulating inflammatory markers				
Adiponectin, *μg/mL*	7.4 (4.4–13.7)	7.8 (4.7–13.0)	0.71	
Leptin, *ng/mL*	8.5 (3.8–17.1)	10.6 (5.2–21.8)	**<0.01**	
IFN-γ, *pg/mL*	0.7 (0.3–1.2)	0.6 (0.4–1.0)	0.97	
IL-1β, *pg/mL*	1.1 (0.5–2.5)	1.0 (0.5–2.1)	0.38	
IL-2, *pg/mL*	1.3 (0.7–2.5)	1.3 (0.7–2.3)	0.39	
IL-4, *pg/mL*	2.3 (1.2–4.1)	2.3 (1.1–4.2)	0.62	
IL-5, *pg/mL*	0.6 (0.3–1.2)	0.6 (0.3–1.1)	0.41	
IL-6, *pg/mL*	1.9 (0.9–4.1)	1.6 (0.9–3.42	0.13	
IL-8, *pg/mL*	10.5 (5.9–20.3)	9.2 (5.3–17.9)	0.10	
IL-10, *pg/mL*	1.4 (0.6–3.0)	0.9 (0.5–1.7)	**<0.001**	
TNF-α, *pg/mL*	2.6 (1.4–6.5)	2.6 (1.2–5.9)	0.41	
CRP, *mg/L*	1.9 (0.6–4.7)	1.8 (0.7–4.3)	0.61	
Summary measure[e]	−0.2 (−0.6–0.3)	−0.6 (−0.2–0.3)	0.49	

Abbreviations: BMI, body mass index; IFN, Interferon; IL, Interleukin; TNF, Tumor neurosis factor; CRP, C-reactive protein.

[a] Values are mean ± SD, n (%) or median (25th–75th percentile). Data were missing for fasting hours (8), education (4), alcohol (17), leptin (1), CRP (3) among NHL cases and controls and for BMI (2,853) and secondary or higher education (2,437) in MEC.

[b] *p*-values from χ^2 test, Students t-test, or Wilcoxon rank sum test.

[c] Comparison based on entire MEC data set excluding “Other” ethnicity (N=203,621)

[d] Matching criteria.

[e] Composite score from principal components analysis of log-transformed IL-1β, IL-4, IL-5, IL-6, IL-8, and TNF-α.

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Table 2

Risk for Non-Hodgkin Lymphoma by tertiles (T1–T3) of circulating markers[a]

Analyte	T1	T2	T3	p_{trend} [b]
Adiponectin, μg/mL	**<5.6**	**5.6–<11.0**	**≥11.0**	
Cases/controls	98/177	84/184	90/180	
OR (95% CI) all	1.00	0.81 (0.55, 1.17)	0.87 (0.58, 1.30)	0.67
OR (95% CI) >1 y only[c]	1.00	0.78 (0.50, 1.19)	0.87 (0.55, 1.36)	0.63
Leptin, ng/ml	**<6.4**	**6.4–<14.9**	**≥14.9**	
Cases/controls	105/166	91/182	76/192	
OR (95% CI) all	1.00	0.72 (0.49, 1.05)	0.48 (0.30, 0.76)	**<0.001**
OR (95% CI) >1 y only[c]	1.00	0.73 (0.48, 1.13)	0.61 (0.37, 1.02)	0.05
IFN-γ, pg/mL	**<0.5**	**0.5–<0.9**	**≥0.9**	
Cases/controls	93/172	80/195	99/174	
OR (95% CI) all	1.00	0.75 (0.51, 1.10)	1.05 (0.72, 1.55)	0.61
OR (95% CI) >1 y only[c]	1.00	0.69 (0.44, 1.06)	1.02 (0.66, 1.57)	0.82
IL-1β, pg/mL	**<0.6**	**0.6–<1.6**	**≥1.6**	
Cases/controls	93/176	83/189	96/176	
OR (95% CI) all	1.00	0.81 (0.54, 1.22)	1.04 (0.69, 1.56)	0.09
OR (95% CI) >1 y only[c]	1.00	1.00 (0.64, 1.56)	1.00 (0.63, 1.60)	0.52
IL-2, pg/mL	**<0.9**	**0.9–<1.9**	**≥1.9**	
Cases/controls	86/182	91/183	95/176	
OR (95% CI) all	1.00	1.07 (0.72, 1.58)	1.16 (0.79, 1.72)	0.14
OR (95% CI) >1 y only[c]	1.00	1.08 (0.69, 1.69)	1.10 (0.70, 1.73)	0.51
IL-4, pg/mL	**<1.4**	**1.4–<3.4**	**≥3.4**	
Cases/controls	87/182	97/177	88/182	
OR (95% CI) all	1.00	1.14 (0.79, 1.65)	1.00 (0.65, 1.55)	0.25
OR (95% CI) >1 y only[c]	1.00	1.26 (0.83, 1.92)	1.01 (0.62, 1.65)	0.53
IL-5, pg/mL	**<0.4**	**0.4–<0.9**	**≥0.9**	
Cases/controls	87/181	87/185	98/175	
OR (95% CI) all	1.00	0.96 (0.60, 1.55)	1.20 (0.71, 2.02)	0.14
OR (95% CI) >1 y only[c]	1.00	1.05 (0.70, 1.58)	1.32 (0.84, 2.07)	0.47
IL-6, pg/mL	**<1.1**	**1.1–<2.7**	**≥2.7**	
Cases/controls	85/187	86/189	101/165	
OR (95% CI) all	1.00	1.02 (0.71, 1.48)	1.39 (0.95, 2.02)	0.17
OR (95% CI) >1 y only[c]	1.00	0.93 (0.62, 1.41)	1.11 (0.72, 1.70)	0.97
IL-8, pg/mL	**<6.7**	**6.7–<14.6**	**≥14.6**	
Cases/controls	79/188	94/179	99/174	
OR (95% CI) all	1.00	1.30 (0.88, 1.91)	1.45 (0.97, 2.16)	0.08
OR (95% CI) >1 y only[c]	1.00	1.08 (0.70, 1.65)	1.21 (0.77, 1.90)	0.26
IL-10, pg/mL	**<0.6**	**0.6–<1.6**	**≥1.6**	

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Analyte	**T1**	**T2**	**T3**	p_{trend} [b]
Cases/controls	68/197	77/194	127/150	
OR (95% CI) all	1.00	1.28 (0.85, 1.94)	3.07 (2.02, 4.66)	**<0.001**
OR (95% CI) >1 y only[c]	1.00	1.07 (0.67, 1.69)	2.20 (1.38, 3.51)	0.06
TNF-α, pg/mL	**<1.7**	**1.7–<4.6**	**≥4.6**	
Cases/controls	95/177	81/191	96/173	
OR (95% CI) all	1.00	0.78 (0.54, 1.14)	1.04 (0.70, 1.54)	0.05
OR (95% CI) >1 y only[c]	1.00	0.73 (0.48, 1.11)	0.98 (0.63, 1.54)	0.23
CRP, mg/L	**<1.0**	**1.1–<3.1**	**≥3.1**	
Cases/controls	92/183	85/178	94/178	
OR (95% CI) all	1.00	0.94 (0.66, 1.36)	1.05 (0.72, 1.52)	0.32
OR (95% CI) >1 y only[c]	1.00	0.78 (0.51, 1.18)	0.85 (0.56, 1.31)	0.70
Summary measure[c]	**<−0.5**	**−0.5–<0.1**	**≥0.1**	
Cases/controls	94/177	81/191	97/173	
OR (95% CI) all	1.00	0.79 (0.53, 1.16)	1.08 (0.73, 1.60)	0.08
OR (95% CI) >1 y only[c]	1.00	0.86 (0.55, 1.36)	1.02 (0.65, 1.60)	0.42

Abbreviations: BMI, body mass index; CRP, C-reactive protein IFN, Interferon; IL, Interleukin; TNF, Tumor neurosis factor

[a] OR and 95% CI estimated by conditional logistic regression; cases and controls matched on sex, birthdate (± 1 year), ethnicity (white, Japanese American, Latino, African American, or Native Hawaiian), location (California or Hawaii), date of blood draw (within ±1 year), time of day of blood draw, and fasting hours prior to blood draw (0–<6, 6–<8, 8–<10, or ≥10). Missing data for leptin (1) and CRP (3).

[b] p for trend based on the Wald χ^2 test of a log-transformed continuous variable.

[c] N=642 (219 cases and 423 controls)

[d] Composite score from principal components analysis of log-transformed IL-1β, IL-4, IL-5, IL-6, IL-8, and TNF-α.

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Table 3

Risk of Non-Hodgkin Lymphoma by tertiles of circulating markers and BMI[a]

	Body Mass Index (BMI)				$p_{interaction}$ [b]
	<25 kg/m^2		25 kg/m^2		
	Cases/controls	**OR (95% CI)**	**Cases/controls**	**OR (95% CI)**	
Leptin, ng/ml					<0.0001
<6.4	65/103	1.00	40/62	1.00	
6.4–<14.9	31/81	0.52 (0.24, 1.09)	60/102	0.84 (0.45, 1.55)	
≥14.9	13/41	0.35 (0.10, 1.18)	63/151	0.54 (0.26, 1.12)	
p_{trend} [c]		0.02		0.02	
IL-10, pg/mL					0.14
<0.64	28/83	1.00	40/114	1.00	
0.64–<1.19	33/77	0.82 (0.34, 1.93)	44/117	0.87 (0.47, 1.62)	
≥1.59	48/66	1.56 (0.65, 3.71)	79/84	2.46 (1.33, 4.54)	
p_{trend} [c]		0.40		<0.01	

Abbreviations: BMI, body mass index; CI, Confidence interval; CRP, C-reactive protein; IFN, Interferon; IL, Interleukin; OR, odds ratio; TNF, Tumor neurosis factor.

[a] OR and 95% CI estimated by conditional logistic regression; cases and controls matched on sex, birthdate (± 1 year), ethnicity (white, Japanese American, Latino, African American, or Native Hawaiian), location (California or Hawaii), date of blood draw (within ±1 year), time of day of blood draw, and fasting hours prior to blood draw (0–<6, 6–<8, 8–<10, or ≥10). Data were missing for leptin (1).

[b] $p_{interaction}$ based on the Wald χ^2 test of the cross-product terms between log-transformed continuous serum measure and continuous BMI.

[c] p_{trend} based on the Wald χ^2 test of a log-transformed continuous variable.

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Table 4

Risk of Non-Hodgkin Lymphoma by years between blood draw and diagnosis[a]

	<2.7 years		2.7 years		$p_{interaction}$ [b]
	Cases/controls	**OR (95% CI)**	**Cases/controls**	**OR (95% CI)**	
Leptin, ng/ml					<0.0001
<6.4	51/80	1.00	54/86	1.00	
6.4–<14.9	52/100	0.64 (0.36–1.15)	39/82	0.69 (0.39–1.23)	
≥14.9	33/97	0.38 (0.19–0.74)	43/95	0.65 (0.33–1.27)	
P_{trend} [c]		<0.01		0.09	
IL-10, pg/mL					
<0.6	26/97	1.00	42/100	1.00	0.92
0.6<1.6	35/92	1.59 (0.83–3.06)	42/102	0.95 (0.52–1.72)	
≥1.6	75/89	3.88 (2.08–7.26)	52/61	1.97 (1.07–3.62)	
P_{trend} [c]		<0.001		0.21	

Abbreviations: BMI, body mass index; CI, Confidence interval; CRP, C-reactive protein IFN, Interferon; IL, Interleukin; OR, odds ratio; TNF, Tumor neurosis factor.

[a] OR and 95% CI estimated by conditional logistic regression; cases and controls matched on sex, birthdate (± 1 year), ethnicity (white, Japanese American, Latino, African American, or Native Hawaiian), location (California or Hawaii), date of blood draw (within ±1 year), time of day of blood draw, and fasting hours prior to blood draw(0–<6, 6–<8, 8–<10, or ≥10). Data were missing for leptin (1).

[b] $p_{interaction}$ based on the Wald χ^2 test of cross-product terms between the log-transformed continuous serum measure and years between blood draw and diagnosis.

[c] p_{trend} based on the Wald χ^2 test of a log-transformed continuous variable.

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Table 5

Risk for DLBCL and FL by tertiles of circulating markers[a]

	DLBCL				FL			
	T1	**T2**	**T3**	p_{trend} [b]	**T1**	**T2**	**T3**	p_{trend} [b]
Adiponectin, μg/mL	**<5.6**	**5.6–<11.0**	**≥11.0**		**<5.6**	**5.6–<11.0**	**≥11.0**	
Cases/controls	28/49	24/57	27/51	.	16/32	19/30	14/34	
OR (95% CI) all	1.00	0.70 (0.33, 1.45)	0.85 (0.40, 1.78)	0.83	1.00	1.19 (0.52, 2.73)	0.82 (0.31, 2.20)	0.80
OR (95% CI) >1 y only[c]	1.00	0.61 (0.27, 1.39)	0.86 (0.39, 1.92)	0.84	1.00	1.06 (0.38, 2.99)	0.50 (0.14, 1.75)	0.35
Leptin, ng/ml	**<6.4**	**6.4–<14.9**	**≥14.9**		**<6.4**	**6.4–<14.9**	**≥14.9**	
Cases/controls	28/45	28/56	23/56	.	17/21	20/34	12/41	
OR (95% CI) all	1.00	0.73 (0.36, 1.50)	0.49 (0.20, 1.24)	0.33	1.00	0.49 (0.17, 1.38)	0.13 (0.03, 0.53)	**<0.01**
OR (95% CI) >1 y only[c]	1.00	0.96 (0.44, 2.13)	0.74 (0.27, 2.00)	0.93	1.00	0.49 (0.13, 1.78)	0.16 (0.03, 0.95)	0.06
IFN-γ, pg/mL	**<0.5**	**0.5–<0.9**	**≥0.9**		**<0.5**	**0.5–<0.9**	**≥0.9**	
Cases/controls	24/52	26/64	29/41	.	20/35	12/28	17/33	
OR (95% CI) all	1.00	0.91 (0.45, 1.82)	1.60 (0.79, 3.26)	0.23	1.00	0.72 (0.28, 1.82)	0.85 (0.33, 2.16)	0.93
OR (95% CI) >1 y only[c]	1.00	0.76 (0.36, 1.60)	1.41 (0.65, 3.06)	0.64	1.00	0.53 (0.17, 1.70)	0.91 (0.31, 2.68)	0.88
IL-1β, pg/mL	**<0.6**	**0.6–<1.6**	**≥1.6**		**<0.6**	**0.6–<1.6**	**≥1.6**	
Cases/controls	23/49	24/59	32/49	.	23/40	10/29	16/27	
OR (95% CI) all	1.00	0.90 (0.43, 1.87)	1.48 (0.72, 3.05)	0.32	1.00	0.56 (0.21, 1.52)	0.99 (0.38, 2.56)	0.07
OR (95% CI) >1 y only[c]	1.00	1.10 (0.50, 2.41)	1.45 (0.64, 3.28)	0.78	1.00	0.97 (0.32, 2.99)	1.19 (0.39, 3.60)	0.13
IL-2, pg/mL	**<0.9**	**0.9–<1.9**	**≥1.9**		**<0.9**	**0.9–<1.9**	**≥1.9**	
Cases/controls	29/52	24/41	26/64	.	17/39	16/29	16/28	
OR (95% CI) all	1.00	1.03 (0.49, 2.17)	0.70 (0.34, 1.41)	0.54	1.00	1.31 (0.53, 3.25)	1.35 (0.53, 3.43)	0.22
OR (95% CI) >1 y only[c]	1.00	0.92 (0.40, 2.12)	0.52 (0.23, 1.17)	0.79	1.00	1.60 (0.53, 4.82)	1.25 (0.38, 4.11)	0.34
IL-4, pg/mL	**<1.4**	**1.4–<3.4**	**≥3.4**		**<1.4**	**1.4–<3.4**	**≥3.4**	
Cases/controls	27/53	25/54	27/50	.	17/40	20/29	12/27	
OR (95% CI) all	1.00	0.93 (0.48, 1.82)	1.10 (0.50, 2.41)	0.61	1.00	1.62 (0.67, 3.89)	1.09 (0.40, 3.01)	0.25
OR (95% CI) >1 y only[c]	1.00	0.86 (0.41, 1.77)	0.96 (0.40, 2.35)	0.31	1.00	1.92 (0.68, 5.45)	1.18 (0.36, 3.83)	0.21
IL-5, pg/mL	**<0.4**	**0.4–<0.9**	**≥0.9**		**<0.4**	**0.4–<0.9**	**≥0.9**	

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	DLBCL				FL			
	T1	**T2**	**T3**	p_{trend} [b]	**T1**	**T2**	**T3**	p_{trend} [b]
Cases/controls	18/50	30/51	31/56	.	17/43	16/27	16/26	
OR (95% CI) all	1	1.84 (0.85, 3.99)	1.79 (0.80, 4.01)	0.92	1	1.67 (0.71, 3.92)	2.12 (0.73, 6.13)	0.05
OR (95% CI) >1 y only[c]	1	2.12 (0.88, 5.12)	2.17 (0.88, 5.32)	0.86	1	1.49 (0.52, 4.26)	1.45 (0.36, 5.80)	0.15
IL-6, pg/mL	**<1.1**	**1.1–<2.7**	**≥2.7**		**<1.1**	**1.1–<2.7**	**≥2.7**	
Cases/controls	25/54	28/55	26/48	.	14/40	19/33	16/23	
OR (95% CI) all	1.00	1.13 (0.58, 2.20)	1.20 (0.58, 2.48)	0.73	1.00	1.71 (0.72, 4.07)	2.05 (0.81, 5.13)	**0.04**
OR (95% CI) >1 y only[c]	1.00	1.17 (0.57, 2.42)	0.82 (0.35, 1.94)	0.54	1.00	1.26 (0.44, 3.57)	2.42 (0.75, 7.80)	0.24
IL-8, pg/mL	**<6.7**	**6.7–<14.6**	**≥14.6**		**<6.7**	**6.7–<14.6**	**≥14.6**	
Cases/controls	20/41	29/63	30/53	.	16/41	16/27	17/28	
OR (95% CI) all	1.00	0.93 (0.45, 1.93)	1.15 (0.56, 2.36)	0.40	1.00	1.61 (0.65, 3.95)	1.70 (0.66, 4.35)	0.13
OR (95% CI) >1 y only[c]	1.00	0.96 (0.45, 2.07)	1.04 (0.48, 2.26)	0.62	1.00	1.70 (0.56, 5.20)	2.92 (0.83,	0.13
IL-10, pg/mL	**<0.6**	**0.6–<1.6**	**≥1.6**		**<0.6**	**0.6–<1.6**	**≥1.6**	
Cases/controls	24/56	20/58	35/43	.	9/46	14/29	26/21	
OR (95% CI) all	1.00	0.80 (0.39, 1.66)	2.36 (1.10, 5.05)	0.06	1.00	4.15 (1.22,	8.46 (2.71,	**0.01**
OR (95% CI) >1 y only[c]	1.00	0.61 (0.28, 1.33)	1.62 (0.71, 3.69)	0.64	1.00	5.11 (1.23,	7.44 (1.97,	0.12
TNF-α, pg/mL	**<1.7**	**1.7–<4.6**	**≥4.6**		**<1.7**	**1.7–<4.6**	**≥4.6**	
Cases/controls	32/42	23/66	24/49	.	17/35	15/27	17/34	
OR (95% CI) all	1.00	0.42 (0.21, 0.85)	0.58 (0.28, 1.22)	0.92	1.00	1.16 (0.46, 2.92)	1.03 (0.41, 2.61)	0.28
OR (95% CI) >1 y only[c]	1.00	0.40 (0.19, 0.84)	0.68 (0.31, 1.51)	0.68	1.00	1.09 (0.36, 3.29)	0.85 (0.28, 2.56)	0.31
CRP, mg/L	**<1.0**	**1.1–<3.1**	**≥3.1**		**<1.0**	**1.1–<3.1**	**≥3.1**	
Cases/controls	30/54	22/52	27/51	.	16/32	17/32	16/32	
OR (95% CI) all	1.00	0.78 (0.41, 1.50)	0.97 (0.49, 1.92)	0.26	1.00	1.03 (0.43, 2.47)	0.96 (0.38, 2.43)	0.64
OR (95% CI) >1 y only[c]	1.00	0.54 (0.26, 1.13)	0.64 (0.30, 1.40)	0.78	1.00	0.97 (0.31, 3.01)	0.85 (0.26, 2.74)	0.84
Summary measure[d]	**<−0.5**	**−0.5–<0.1**	**≥0.1**		**<−0.5**	**−0.5–<0.1**	**≥0.1**	
Cases/controls	24/53	28/54	27/50	.	20/42	14/25	15/29	
OR (95% CI) all	1.00	1.15 (0.59, 2.25)	1.23 (0.60, 2.50)	0.60	1.00	1.22 (0.51, 2.92)	1.09 (0.45, 2.62)	0.10
OR (95% CI) >1 y only[c]	1.00	0.78 (0.38, 1.59)	1.04 (0.46, 2.33)	0.95	1.00	1.11 (0.37, 3.28)	1.04 (0.36, 3.01)	0.17

Abbrev: DLBCL, diffuse large B-cell lymphoma; BMI, body mass index; CRP, C-reactive protein IFN, Interferon; IL, Interleukin; TNF, Tumor neurosis factor.

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[a] OR and 95% CI estimated by conditional logistic regression; cases and controls matched on sex, birthdate (± 1 year), ethnicity, location (California or Hawaii), date of blood draw (within ±1 year), time of day of blood draw, and fasting hours prior to blood draw (0–<6, 6–<8, 8–<10, or ≥10).

[b] p_{trend} based on the Wald χ^2 test of a log-transformed continuous variable.

[c] N=198 (66 cases and 132 controls) for DLBCL and N=97 (33 cases and 64 controls) for follicular lymphoma

[d] Composite score from principal components analysis of log-transformed IL-1β, IL-4, IL-5, IL-6, IL-8, and TNF-α.

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