Research Article

Circulating Soluble CD30 and Future Risk of Lymphoma; Evidence from Two Prospective Studies in the General Population

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Abstract

Background: Elevated circulating soluble CD30 (sCD30) has been previously associated with AIDS-related non-Hodgkin lymphoma (NHL) risk. This finding was recently extended to the general population where elevated levels of sCD30 were reported in prediagnostic serum among subjects that developed NHL later in life.

Methods: We carried out a replication study within the Italian European Prospective Investigation into Cancer and Nutrition cohort. Plasma sCD30 concentration was measured by ELISA in prospectively collected blood of 35 B-cell lymphoma cases and 36 matched controls.

Results: We observed significantly increased relative risks for lymphoma with increasing sCD30 levels [OR (95% CI) for second and third tertiles vs. first tertile: 5.5 (1.5–20.2), 4.0 (1.1–13.9), respectively]. In addition, spline analyses showed that the dose–response curve of sCD30 and lymphoma risk was monotonic and quite similar to the risks reported in the previous study.

Conclusion: This replication study adds to the evidence that sCD30 is related to future lymphoma risk in a concentration-dependent manner in the general population.

Impact: The results of this study strengthen the observation that chronic sustained B-cell activation plays an important role in lymphomagenesis. *Cancer Epidemiol Biomarkers Prev; 20(9); 1925–7. ©2011 AACR.*

Lymphoma risk has been related to genetic variation in genes encoding for cytokines that modulate the inflammatory process or are associated with B-cell activation (1). Consistent with these findings, studies among HIV patients have shown that serum cytokines and sCD30, a marker for chronic B-cell stimulation (2) are associated with lymphoma risk (1, 3). Recently, the finding that prospectively measured sCD30 is related to lymphoma risk has been extended to the general population. Purdue and colleagues (4) reported elevated sCD30 levels in prediagnostic serum of healthy subjects that later in life developed non-Hodgkin lymphoma (NHL). Replication of these results would provide strong evidence of chronic sustained B-cell activation as a major contributor to lymphomagenesis in the general population. This would facilitate further exploration of mechanisms involved in lymphomagenesis and could provide possibilities for early screening. We report here on a replication study within the Italian European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.

A detailed description of the EPIC cohort study can be found elsewhere (5). In the period 1993 to 1998, EPIC Italy completed the recruitment of 47,749 volunteers in 4 different areas covered by cancer registries (6). This study included incident cases of B-cell lymphoma diagnosed through 2006, excluding cases in the first 2 years of follow-up. Lymphoma was defined based on the World Health Organization classification system for lymphoid malignancies and includes all B-cell lymphomas (7, 8). A total of 86 patients with B-cell lymphoma were eligible, of which only 36 had adequate plasma volumes for sCD30 analyses. Controls (n = 36) were frequency-matched to the cases on age at baseline and sex. Cases with and without adequate plasma volumes were similar with regard to sex, age, and lymphoma subtype distribution. Ethical approval for this study has been obtained from all participating centers and the IARC Internal Review Board, and all participants provided written informed consent in accordance with the Declaration of Helsinki.

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Blood samples were all collected in the morning after fasting and were stored at −196°C until laboratory analyses. All plasma specimens were thawed once before analyses. Plasma sCD30 was measured by ELISA (Bender Medsystems) according to the manufacturer's protocol. Duplicate analyses indicated an assay variation coefficient of 7%. Laboratory personnel were blinded with regard to case–control status.

The Wilcoxon rank-sum test was used to test for significant differences in plasma sCD30 concentration between cases and controls. ORs and 95% CIs relating sCD30 concentration categories and lymphoma risk were computed using logistic regression modeling. sCD30 concentration was categorized based on the tertiles of the overall distribution. We additionally analyzed the data using generalized additive modeling with logistic regression to explore the shape of the concentration–response relation in more detail. For calculating the ORs and CIs for the relation between sCD30 and lymphoma case–control status from these models, we used the approach described by Figueires and Cadarso-Suarez (9). Logistic models were adjusted for age at baseline, body mass index (BMI), and sex. All statistical tests were 2-sided, with a $P < 0.05$ considered as statistically significant.

Of the 72 plasma samples, 71 were analyzed successfully. Cases ($n = 35$) and controls ($n = 36$) had identical distributions of matching variables (Table 1). Mean

sCD30 concentration among controls and cases was 20.9 (SD 11.2; median 17.9) and 24.6 (SD 11.8; median 20.5) ng/mL, respectively (18% increase; P value 0.04). Increased sCD30 levels relative to controls were observed for cases with less and more than 6 years (median) between time of blood draw and case diagnosis. No association was observed between sCD30 concentrations and time between blood draw and case diagnosis ($P = 0.9$). Elevated sCD30 concentration was strongly associated with subsequent lymphoma risk, with ORs of 5.5 (95% CI: 1.5–20.2) and 4.0 (95% CI: 1.1–13.9) for the second and third tertiles versus the first. Additional spline analyses revealed that there was a monotonic increase in risk with increasing sCD30 concentrations, indicating that the flat dose–response in the categorical analysis is consistent with a monotonically increasing trend (Fig. 1). The data did not allow analyses by lymphoma subtype; however, mean sCD30 concentrations among lymphoma subtypes were all higher than controls except for multiple myeloma which had an average of 18.8 (SD 4.1) ng/mL. Removing multiple myeloma ($n = 7$) from the case set, however, did not change the overall findings except that results became statistically more significant.

Purdue and colleagues (4) previously reported that serum sCD30 is associated with an increased risk of NHL in the prospective Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Our study, nested within the prospective Italian EPIC cohort, was small but reasonably powered to replicate the initial findings of Purdue

Table 1. Selected baseline characteristics of lymphoma cases and control subjects

Characteristics	Cases ($n = 35$)	Controls ($n = 36$)
Age at enrollment; mean (SD)	53.8 (8.1)	53.7 (7.5)
BMI; mean (SD)	26.3 (3.6)	25.8 (3.0)
Sex		
Male; n (%)	13 (37.1)	14 (38.9)
Female; n (%)	22 (62.9)	22 (61.1)
Histologic subtype of lymphoma; n (%)		
Follicular lymphoma	6 (17.1)	
Diffuse large B-cell lymphoma	8 (22.9)	
Multiple myeloma	7 (20.0)	
Mantle cell lymphoma	2 (5.7)	
Chronic lymphocytic leukemia	3 (8.6)	
Other/NOS	9 (25.7)	
sCD30 concentration; ng/mL		
Mean (SD); all	24.6 (11.8)	20.9 (11.2)
Mean (SD); 2–6 years to diagnosis ($n = 18$)	26.4 (14.5)	
Mean (SD); > 6 years to diagnosis ($n = 17$)	22.8 (8.1)	
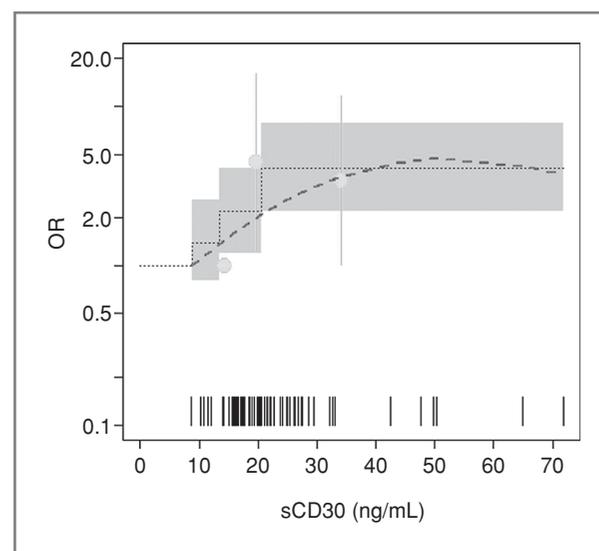
Figure 1. Relation between circulating sCD30 and risk of lymphoma. Displayed are the results from a categorical analysis using tertiles of the plasma concentration distribution (cyan, point estimate + 95% CI plotted at the mean plasma concentration of each tertile) and the estimated concentration–response relation from a generalized additive model (dashed red line). Point estimates (dotted line) and CI (shaded grey) from the categorical analysis published in Purdue and colleagues (4) are included for comparison.

and colleagues (Ref. 4; power 0.7, alpha = 0.05). Our results not only confirm that sCD30 is associated with future risk of B-cell lymphoma but also show that the 2 studies have comparable concentration dependent risks. These risks do not seem to be influenced by time between blood collection and diagnosis. Similar to the Purdue and colleagues (4) study the association between sCD30 concentration and subsequent lymphoma risk seems to be apparent even more than 6 years after blood collection. This replication study adds therefore support to the notion that sCD30, as measured in prediagnostic serum/plasma, is related to future risk of B-cell lymphoma in the general population. This provides evidence that B-cell activation, the tumor necrosis factor (TNF) receptor superfamily, and/or predisposition toward a Th2-response are important phenomena in lymphomagenesis as sCD30 plays an important role in these pathways (10–12). Future studies should focus on determinants of sCD30 and the further exploration of B-cell activation, TNF, and Th2-oriented pathways to further elucidate the involvement of sCD30 itself and these pathways in lymphomagenesis.

Disclosure of Potential Conflicts of Interest

The authors declare no competing financial interests.

Authors Contributions

Acknowledgments

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