Immune Dysregulation Is Associated With Greater Risk of Non-Hodgkin Lymphoma

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Altered immunity is a well-established cause of non-Hodgkin lymphoma (NHL) – as evidenced by increased rates of NHL among transplant recipients and persons with HIV. Hyperactivation of B-cells, a type of lymphocyte that is produced in the bone marrow and helps fight infection, is commonly seen in persons with HIV and is thought to play a role in lymphomagenesis in this population. However, the importance of B-cell activation in the development of NHL cases occurring in the general population has not been widely investigated.

Recently, Dr. Anneclaire De Roos of the Public Health Sciences Division Epidemiology Program, led a case-control study within the Women's Health Initiative Observational Study cohort of healthy postmenopausal women to measure biomarkers of B-cell activation in blood samples collected from 491 cases of B-cell NHL and 491 controls matched on age, geographic region and date of study enrollment. Specifically, the authors measured levels of five immune-regulated molecules an average of six years prior to NHL diagnosis: a cytokine-like molecule (sCD23), two soluble cytokine receptors (sCD27, sCD30), a molecule involved in lymphocyte activation (sCD44) and a B-cell stimulatory chemokine (CXCL13).

Each of the immune markers investigated was significantly associated with increased risk of B-cell NHL. There was no evidence of confounding by race/ethnicity, education, body mass index or smoking status. Compared to women in the lowest expression quartile, women with marker levels in the highest expression quartiles of CD23, CD27, CD30 or CXCL13 had a 2.8 to 5.5-fold increased risk of B-cell NHL. Further, there was a trend of increasing NHL risk with increasing levels of each marker. The association between CD44 and NHL risk was not as clear as for the other markers.

Compared to women without high levels of any of the markers, women in the highest quartile for any one of the five markers had a 1.9 [95% Confidence Interval (CI): 1.3-2.8] fold increased risk of B-cell NHL, and the relative risk increased with each additional elevated marker, such that women with elevated levels of all five markers had a 10-fold increase in risk [Odds Ratio: 10.0, 95% CI: 2.0-20.2].

The authors also investigated specific subtypes of B-cell NHL and found that CD23, CD27, CD30 and CXCL13 were associated with a higher risk of all major subtypes of B-cell NHL (see Figure), suggesting that the association between B-cell activation and NHL is not limited to the aggressive forms of NHL that predominate in HIV. Overall, the strength of the observed associations was attenuated by a longer time between blood draw and NHL diagnosis. The associations were strongest for cases with <3 years between blood draw and diagnosis; however, some significant associations were also detected among cases with a prediagnostic lag time of 9-13 years.

Given that these findings suggest a prominent role for B-cell activation either in the development of B-cell NHL or in the processes reflective of early disease development, prospective studies to better understand this biological pathway and its implications for the development of predictive markers will be anticipated with great interest.

De Roos AJ, Mirick DK, Edlefsen KL, Lacroix AZ, Kopecky KJ, Madeleine MM, Magpantay L, Martinez-Maza O. (2012). Markers of B-cell activation in relation to risk of non-Hodgkin Lymphoma. *Cancer Research*. Jul 30. [Epub ahead of print] doi: 10.1158/0008-5472.CAN-12-1639
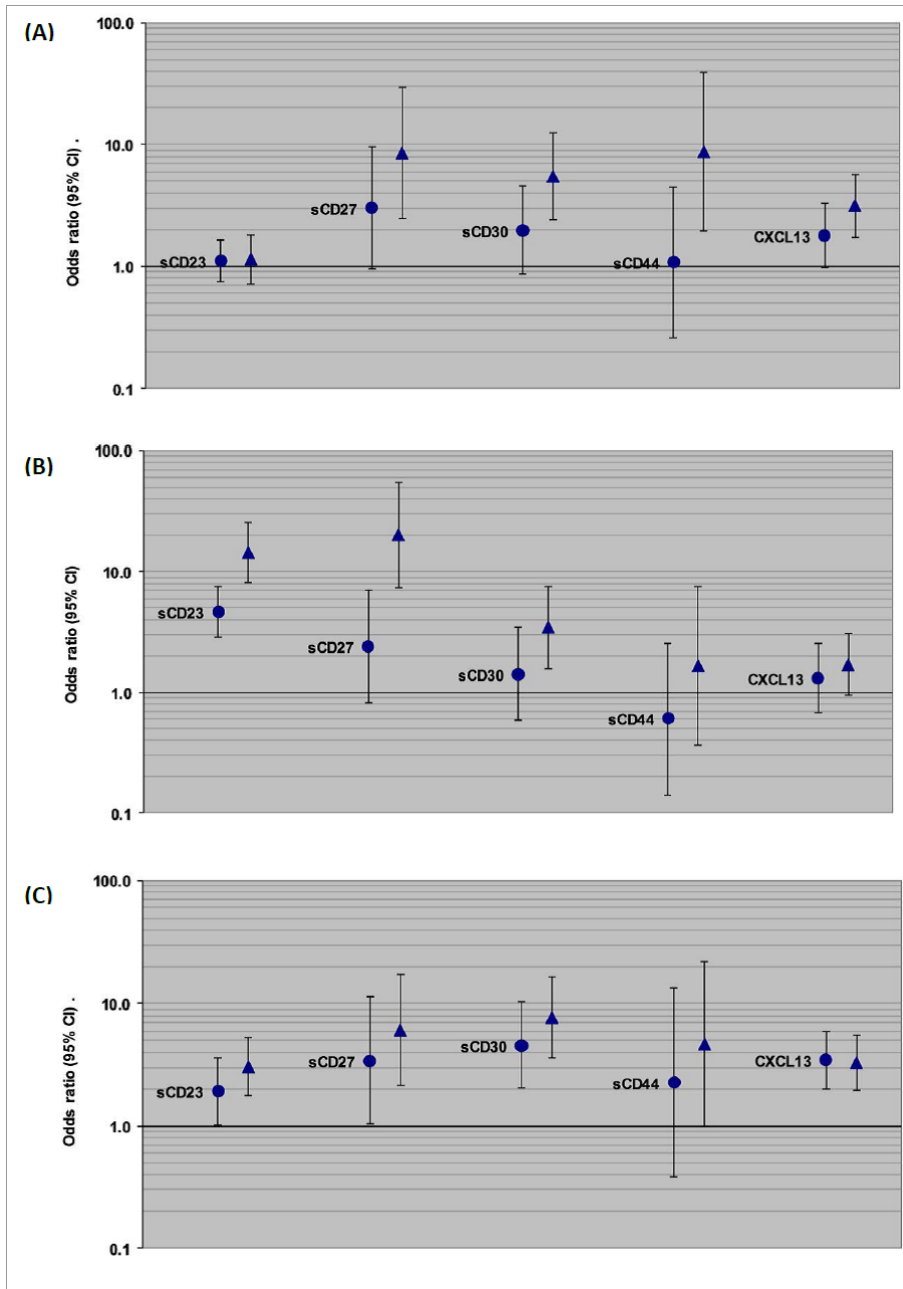
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Figure 1. (A) Chronic lympocytic leukemia/small lympocytic leukemia/prolymphocytic leukemia risk associated with 1-unit (natural log scale) increase in immune marker level (OR and 95% CI). (B) Diffuse large B-cell lymphoma risk associated with 1-unit (natural log scale) increase in immune marker level (OR and 95% CI). (C) follicular lymphoma risk associated with 1-unit (natural log scale) increase in immune marker level (OR and 95% CI). Cases are categorized by decreasing lag time between blood draw and diagnosis (circle: 9-13 years; triangle: <3 years).