GERMAN CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

No. 76 December 15, 2005 (JL)

The Role of Genes in the Development of Non-Hodgkin's Lymphomas

Individual genetic variations increase the risk of developing non-Hodgkin's lymphoma

An international consortium of epidemiologists – including **Dr. Alexandra Nieters** and **Professor Nikolaus Becker** of the Clinical Epidemiology Division of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) – has conducted the first ever investigation of genetic factors in the development of non-Hodgkin's lymphoma (NHL) in a study called InterLymph. The researchers collaborating within the International Lymphoma Epidemiology Consortium have found out that variations of individual DNA building blocks in genes encoding for the cellular signaling molecules tumor necrosis factor (TNF) and interleukin 10 (IL-10) increase the risk of developing non-Hodgkin's lymphoma.

The study is a step towards developing a deeper understanding of the development of lymphomas, which may lead to novel prevention and treatment approaches in the future. The researchers have now published their results online in the journal *Lancet Oncology**.

The study is based on data gathered in eight case-control studies from different countries involving a total of 3586 NHL patients and 4018 healthy individuals as control group. The epidemiologists focused their attention on 12 different variations of single DNA building blocks, called single nucleotide polymorphisms, which are located in genes whose products regulate important functions in immune response and anti-inflammatory reaction. For two variations concerning the genes for (i) tumor necrosis factor and (ii) interleukin, the investigators found an elevated individual risk of non-Hodgkin's lymphoma. Analyzing different NHL subtypes, they discovered that the two gene variations specifically increase the risk of diffuse large B-cell lymphoma, the most common type of malignant lymphoma. The disease risk of individuals carrying one copy of the rare polymorphism in the TNF gene is elevated by 29 percent; a second copy increases the risk by 65 percent. A combination of both gene variants in TNF and IL-10 leads to a 100 percent increase of individual risk. The risk of follicular lymphoma, a generally less aggressive type of lymphoma, is not influenced by the combination of these variants.

In recent years, lymphoma research has focused primarily on the search for environmental or lifestyle risk factors. The study now published is an important step towards a deeper understanding also of genetic factors in NHL development. "We have had two hits in twelve factors we investigated. Now the real work starts, because we are planning to study not only the influence of genetic factors on the development of non-Hodgkin's lymphomas, but also on lymphomas in general. Basically, we are interested here in all genes that influence signaling pathways within the cell such as in inflammatory processes or cellular DNA repair mechanisms," states Alexandra Nieters, assessing the relevance of the study for lymphoma research. In the future, epidemiologists are planning to put more emphasis on combined investigations of genetic and environmental factors in lymphoma development.

The study underlines the importance of international collaboration in the search for genetic causes of chronic diseases: It only became possible by pooling several studies from different countries. This was the only way to obtain a sufficient number of participants to provide statistically supported effects, which could not have been obtained based on the individual studies.

Established in 2002, the InterLymph Consortium is a collaboration of researchers from the United States, Canada, Australia, Germany, Italy, U.K., France, Spain, Ireland, Czechia, Sweden and Denmark who are jointly searching for possible causes and risk factors of

cancers of the lymphatic system. There are plans to extend the collaboration to include Asian and African countries.

Lymphomas are divided into two main types: Hodgkin's disease and non-Hodgkin's lymphomas (NHL). Non-Hodgkin's lymphomas include many variations of lymphatic cancers, which differ strongly in tissue structure and disease progression. In Germany, approximately 13,000 people are diagnosed with NHL each year, more that 5,000 die of it each year.

This project of the Interlymph Consortium is funded by the José Carreras International Leukemia Foundation and the Federal Office for Radiation Protection.

**Nathaniel Rothman, Christine F. Skibola, Sophia S. Wang, et al., and Alexandra Nieters: "Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: a report from the InterLymph Consortium", Lancet Oncology, published online on 29th November 2005 / DOI: 10.1016/S1470-2045(05)70434-4*

This press release is available at www.dkfz.de/pressemitteilungen

Dr. Julia Rautenstrauch
Division of Press and Public Relations
Deutsches Krebsforschungszentrum
Im Neuenheimer Feld 280
D-69120 Heidelberg
T: +49 6221 42 2854
F: +49 6221 42 2968