CEBP Focus: Update on Lymphoma

Environmental and Behavioral Factors and the Risk of Non-Hodgkin Lymphoma

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Investigators around the world have reported that incidence and mortality rates for non-Hodgkin lymphoma (NHL) increased steadily and substantially over the last five decades of the 20th century. Identifying what changes in the environment or in behavior fueled this epidemic still presents a major challenge for cancer epidemiology. In April 2006, a symposium was held at the Annual Meeting of the InterLymph Consortium to discuss the role of environment in NHL risk. Papers from that meeting are presented in this issue and, in summary, show that several environmental and behavioral factors alter the risk of developing lymphoma and may have contributed to the long-term increase in rates. Our current understanding, although quite incomplete, represents real progress, much of it deriving from epidemiologic studies of the last decade and many represented in the InterLymph Consortium.

Several infectious agents cause lymphomas, some by directly transforming normal lymphocytes, some by causing an immunodeficiency syndrome, and some through chronic immune stimulation (Engels). Some infectious agents seem to cause specific forms of lymphoma, such as EBV causing Burkitt or extranodal natural killer/T-cell lymphoma; human herpes virus 8 leading to primary effusion lymphoma; and human T-lymphotrophic virus type I causing adult T-cell leukemia/lymphoma. Chronic immune stimulation may have either highly specific effects (e.g., *H. pylori* and its association with mucosa-associated gastric lymphomas) or more general effects (e.g., hepatitis C virus). HIV is important in several forms of lymphoma, and successful treatment of the infection markedly reduces lymphoma risk. Current work focuses on understanding modes of action, surveillance for undiscovered agents, and evaluation of interactions with common variants in immune-related genes.

Numerous occupations rather consistently appear more often among histories of lymphoma patients than among their peers (Boffetta and deVocht). Many studies show increased risks among farmers, teachers, printers, and wood workers and may represent occupational groups at risk of NHL, even without a known causal agent. It seems less certain, but likely, that meat workers, painters, electrical engineers, and health care workers also are at increased risk of developing NHL. Boffetta and deVoct advocate increased development and use of biomarkers and other measures to assess occupational exposures more sensitively and specifically.

Although no single environmental chemical exposure has been convincingly established as a cause of NHL, several occupational and environmental chemical exposures have emerged as likely candidates, including benzene (Smith et al., Vineis et al.) and polychlorinated biphenyls (Engel et al.). These may be important to the etiology of NHL, but their relevance to the epidemic is less certain. Many workers encounter low levels of benzene (>0.1 ppm) in petroleum refineries, natural gas production, and fuel and solvent distribution. Studies of occupations with probable benzene exposure report varying relative risks of lymphoma, with typical values for more heavily exposed workers well above the null but lower than relative risks for leukemia (Smith et al.). Shortly after workers began accumulating substantial exposures to benzene, numerous observers reported a dramatic excess of leukemia and related diseases of the bone marrow. Many researchers hypothesized that lymphoma would increase as well, but studies showed that mature B cells were less susceptible than bone marrow to damage from benzene. A strikingly similar history of research occurred for ionizing radiation and lymphoma. Longer observation and more refined exposure assessments now show that both benzene and radiation probably cause lymphomas, but the risks at particular dose levels remain uncertain. Work by Vineis et al., reported in this issue, also suggests that a family history of autoimmune disease or malignant hematologic neoplasms predisposes to benzene-induced NHL. Current research focuses on understanding whether benzene might act through toxicity to the immune system generally or through chromosomal translocations, deletions, or other damage (Vineis et al.). Both epidemiology and laboratory work will be required to move the field forward.

Another family of environmental chemicals implicated in lymphoma are the polychlorinated biphenyls and related compounds (Engel, Lan, and Rothman). For polychlorinated biphenyls, dioxins, furans, and organochlorine pesticides, the most convincing evidence for an association with lymphoma comes from the biobank studies. Taken together, the published studies strongly support an association between lymphoma risk and blood levels in advance of diagnosis and, yet, the specific effects of individual compounds vary widely from study to study. The variability may reflect the correlation among exposures and some degree of inaccuracy of assessment, prompting a recommendation by these authors for more precise data on timing of exposure, more observations, and the exploitation of unusual opportunities to disentangle the effects of individual compounds.

Yet another group of agents, solvents, especially chlorinated solvents, remain suspect and deserve scrutiny in both case-control and prospective cohorts (Vineis, Miligi, and Costantini).

Although the iatrogenic lymphomas represent a minority of cases, they may serve as excellent model systems (Krishnan

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and Morgan). Radiation therapy increases NHL risk, albeit less than leukemia risk. Chemotherapy has a stronger effect, presumably through greater damage to DNA, and may serve as a model of chemically induced lymphoma. Finally, immunosuppressive therapy shows the most profound effect, indeed one of the most strikingly immediate effects seen in cancer epidemiology. The model of therapeutic immunosuppression inducing lymphomagenesis has found a parallel in many other immunosuppressed conditions. The DNA repair hypothesis has been explored less, and further research in that area may be instructive.

Diet, physical activity, and body mass all have been suggested to alter lymphoma risk but the results to date are quite inconsistent, despite numerous studies (Skibola). Based on a number of case-control and prospective cohort studies, being overweight (obese) probably increases the risk of NHL and, conversely, moderate physical activity may reduce risk. Several studies support an inverse association between vegetable intake and NHL risk, particularly for the consumption of cruciferous vegetables. These associations may be examined further through the use of multiple study designs (especially favoring prospective data), detailed data on interrelated lifestyle factors, and examinations of gene-environment interaction. Most probably, a mix of smaller mechanistic studies and large pooled analyses of either multiple case-control studies or multiple cohort studies would be fruitful.

Sunlight seems to be consistently, but not strongly, related to a decreased risk of lymphoma (Armstrong and Kricker). Because the degree of protection is not large, data pooling offers a valuable method to examine subgroups and to clarify whether the effects vary with latitude or with ethnicity. Most importantly, studies are needed to propose and test mechanisms of action (e.g., through vitamin D).

In short, lifestyle and behavior offer some promise as ways to modify risk of lymphoma, but the effects still need to be established and the mechanisms of action established. In essence, each probable harmful exposure (e.g., infections, chemicals, and radiation) and each potentially protective factor (e.g., sunlight, vegetables, and physical activity) require specific steps to advance understanding. Several overarching themes recur, including a need to improve exposure assessments by finding more direct measures of the biological mechanisms. In addition, great progress may be made if we evaluate the effects of exposures in conjunction with assessment of the *relevant* susceptibility alleles. Finally, by distinguishing the effects on specific subtypes of lymphoma, we are likely to find that particular agents can cause some lymphomas while having little or no influence on others; without the requisite ability to separate lymphomas into homogeneous classes, we will estimate only overall risks and find them attenuated or miss them altogether.

We may not learn entirely what created the slow-moving lymphoma epidemic, but we expect to see accelerating progress in understanding etiology. Individual studies will permit investigators to devise, test, and refine methods for monitoring exposure. Consortia will permit the large-scale analyses needed to recognize genetic susceptibility variants. Indeed, the InterLymph consortium has already made progress in this regard. All studies will evaluate findings in relation to specific types of lymphoma, even as the capacity to define homogeneous subtypes continues to improve.

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