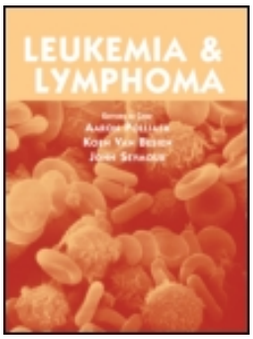

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COMMENTARY

Smoking and lymphoma: a small part of a complex story

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Although decades of research have shown that tobacco is not a major contributor to hematologic malignancies, today cigarette smoking is recognized as a causal agent of myeloid leukemia [1], and the evidence for Hodgkin lymphoma is suggestive [2]. However, a meta-analysis reported in this issue of the journal [3] joins a body of literature that supports at most a weak effect – or possibly none at all – of cigarette smoking on risk of non-Hodgkin lymphoma (NHL). Castillo and Dalia [3] combined data from 24 studies of cigarette smoking and NHL risk and report hints of an association, with a statistically significant 40% increase in NHL risk among current female smokers in case–control studies; however, no truly compelling story has emerged. It seems that novel approaches are still needed to understand whether there is, in fact, a story to tell about the association between cigarette smoking and NHL. Although any NHL risk associated with cigarette smoking is likely to be small, further research to pursue the association is warranted because of the potential for providing insight into the complex etiology of NHL – which has proven elusive outside of severe immunosuppression, certain infections and inherited susceptibility – and because the prevalence of smoking remains high worldwide.

One promising direction for investigation includes refining our understanding of the carcinogens in cigarette smoke and their biological effects that could plausibly contribute to lymphomagenesis. Cigarette smoke contains thousands of chemical constituents, including a number of known carcinogens such as polycyclic aromatic hydrocarbons, *N*-nitrosamines and aromatic amines [4]. Also present is benzene, a known leukemogen that could help explain the established relationship between smoking and myeloid leukemias [5–8]. The promise of this line of research was suggested in a case–control study that found a stronger effect of blond tobacco (which contains more benzene and polycyclic aromatic hydrocarbons) than of black tobacco (which contains more aromatic amines and nitrosamines) on NHL risk [9].

A better understanding of the biologic effects of cigarette smoke may also help us to understand the story more completely. One study has reported increased occurrence of the t(14;18) chromosomal translocation, one of the most common cytogenetic abnormalities in NHL, in lymphocytes of smokers [10]. The possibility of this translocation playing a role in smoking-related lymphomas seemed even more plausible when some studies suggested a particular association between smoking and follicular lymphomas, $>90\%$ of which carry the t(14;18) [11]. However, the few small studies that have explicitly evaluated smoking and t(14;18)-positive lymphomas have not supported this association [12–15], and not all studies support a specific association with follicular lymphoma. Metabolomics is another novel molecular tool that may improve our understanding of the effects of smoking on NHL risk, by evaluating the biochemical profiles of lymphocytes exposed *in vitro* to cigarette smoke or by comparing profiles of smokers and non-smokers [16,17]. Finally, understanding the biologic effects of cigarette smoking on the immune system may provide further clues regarding the relevance of exposure for lymphoma risk.

Alternatively, identification of inherited genetic variations that mediate susceptibility to the adverse effects of smoking may help us understand whether smoking plays a role in NHL. Risks for several cancers are higher among individuals who carry particular alleles of cytochrome P-450 enzymes, which activate carcinogens in cigarette smoke and directly impact the formation of DNA adducts [18,19]. Broader investigation of other key pathways such as DNA repair, inflammation and oxidative stress, which also mediate responses to chemicals in cigarette smoke, may also help identify individuals who are susceptible to lymphomagenesis following exposure.

From the public health perspective, the contribution of tobacco to hematologic malignancies is dwarfed by its role in millions of deaths worldwide each year from other cancers, heart disease, stroke, pulmonary disease and a range of other serious conditions [20]. The tobacco-related public health challenges will persist for decades, because adverse health effects may occur years after exposure, declines in the prevalence of smoking in many developed countries appear to have slowed or stalled in some countries [21], and smoking rates remain high in many other countries and are increasing

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among women and in developing countries. Underscoring the magnitude of the problem, recent surveys indicate that almost two-thirds of adult males in East Asia and the Pacific are current smokers [1]. Despite uncertainties regarding the role of cigarette smoking in NHL, the myriad established adverse effects of tobacco and demonstrable benefits of cessation stress the need for clinicians to recommend the most current, effective measures for achieving long-term abstinence among their patients [22].

Potential conflict of interest: A disclosure form provided by the author is available with the full text of this article at www.informahealthcare.com/lal.

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