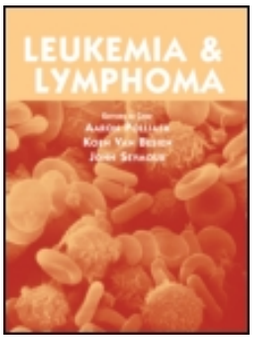

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Brian C.-H. Chiu & Sonali M. Smith

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COMMENTARY

Toward a global understanding of lymphoma: epidemiologic clues from the second most populous country

Brian C.-H. Chiu[1] & Sonali M. Smith[2]

[1]*Department of Health Studies, and* [2]*Section of Hematology/Oncology, University of Chicago, Chicago, IL, USA*

Observations of global and regional geographic variation offer important clues to the etiology and, perhaps, biology of disease. In cancer, this is most explicitly seen in non-Hodgkin lymphoma (NHL) where there is substantial variation in both incidence and histologic subtypes around the world. NHL comprises many clinically, histologically and biologically distinctive lymphoid malignancies. The highest incidence rates are observed in North America and Australia, followed by Europe, with lower rates reported in Asia [1]. From 2005 to 2009, the annual age-adjusted incidence rate in the United States was 19.6 per 100 000 persons, and although the overall incidence has been stable for the past decade, incidence patterns for specific subtypes vary [2]. In contrast, the overall incidence of lymphomas in Asian countries is lower, and ranges from 2.1 (China) and 2.4 (India) to 5.1 (Japan) per 100 000 persons [1]. There are also marked differences in the distribution of lymphoma subtypes across geographic regions. Compared with North America and Western European countries, Asian countries tend to have higher incidences of mature T-/natural killer (NK)-cell lymphomas and extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type (MALT lymphoma) and lower rates of follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and Hodgkin lymphoma [3–7]. It has been proposed that some Epstein–Barr virus (EBV)-associated subtypes of T/NK-cell lymphomas are unique to Asian countries and do not exist in other locales. This geographic and ethnic heterogeneity is well recognized but remains unexplained, mainly because the etiology of lymphoma is largely unknown, although genetic, immune, infectious, environmental and lifestyle factors have been considered as potential risk factors [8]. Nevertheless, examining patterns of specific lymphoma subtypes across different racial/ethnic groups or countries offers important clues regarding the study of lymphoma etiology.

In this issue of ***Leukemia and Lymphoma***, Arora and colleagues [9] review the histological material of over 5000 patients with lymphoma seen at a tertiary care center in South India over a 10-year period of time (2001–2010). This is the first large-scale catalog and description of lymphoma subtypes from the second most populous country in the world. Importantly, the authors describe the subtype distribution according to the most current classification, the 2008 World Health Organization classification of lymphoid neoplasms. In their series, 21.3% had Hodgkin lymphoma (HL) and 78.7% had NHL. For HL, in contrast to Western populations, the authors reported no bimodal age curve and a higher frequency of mixed cellularity (45%) than nodular sclerosis subtype (36%). Of the NHLs, about 79% were B-cell and 20% were T-cell/NK-cell. The most common NHL was diffuse large B-cell lymphoma, which constituted 47% of NHLs, followed by follicular lymphoma (11%). The more common occurrence of aggressive lymphomas countered by decreased frequency of indolent lymphomas is consistent with observations from other Asian countries, and is possibly related to environmental and/or infectious factors. Extranodal primaries accounted for 33% of NHLs and most frequently involved the gastrointestinal tract.

There are several key strengths to this report, including the central review of slides by pathologists and additional immunostains in cases where there were disagreements on the original diagnosis. As mentioned above, this is an impressive and large series from a single tertiary care center in a country where subtypes of lymphoma, in comparison to other Asian countries, have not been well described. However, this strength also brings limitations, as a tertiary hospital population has inherent referral bias. The frequency of a specific lymphoma subtype may be distorted if its underlying pathogenesis is associated with socioeconomic status and environmental or lifestyle factors. In addition, this is a hospital-based analysis and not a population-based analysis. Consequently, a direct comparison of the distribution of subtypes across hospital-based series or different ethnic/racial groups is difficult as the actual incidence rate is not available. Furthermore, the Indian population is a mix of several ancient ethnicities, with Indo-Aryan groups

Correspondence: Sonali M. Smith, MD, Associate Professor, Section of Hematology/Oncology, Director, Lymphoma Program, The University of Chicago, 5841 S. Maryland Avenue, MC2115, Chicago, IL 60637, USA. Tel: 773-834-2895. Fax: 773-702-0963. E-mail: smsmith@medicine.bsd.uchicago.edu

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primarily in the north and Dravidian groups primarily in the south, which may also influence NHL patterns between these two regions [10]. Nevertheless, the current study highlights the importance of continued epidemiologic research to identify lymphoma etiology.

Genetic factors have been linked to the development of lymphoma, including follicular lymphoma and diffuse large B-cell lymphoma [11,12]. On the other hand, evidence from epidemiologic studies suggests that environmental and lifestyle factors might be more important than genetic factors for some subtypes of lymphoma such as HL [13,14] and follicular lymphoma [15,16]. For example, the incidence of follicular lymphoma increases in Asian Indians living in Western countries. The distribution and the male to female ratio of several subtypes in the study by Arora *et al*. [9] differ from those reported for Asian Indians living in the United States based on the Surveillance, Epidemiology and End Results cancer registry [16], further supporting the importance of environmental and lifestyle factors in the development of lymphoma. Interestingly, healthy Indians were found to have a lower frequency of t(14;18)(q32;q21) and t(11;14) chromosomal translocations, genetic hallmarks of follicular lymphoma/diffuse large B-cell lymphoma and mantle cell lymphoma, respectively, than Western populations [17]. However, chromosomal translocations alone are not sufficient, and genetic mutations or environmental exposures may be important in giving rise to additional changes necessary for the development of NHL [15,18]. Cumulative evidence from descriptive and analytic epidemiologic studies supports both etiologic commonality and heterogeneity for lymphoma subtypes [2,19]. The article by Arora *et al*. [9] reinforces the critical need for continued epidemiologic research to rigorously evaluate the interplay between genetic host status, environmental and lifestyle factors, and immune function in NHL etiology.

Despite the caveats described above, the article by Arora *et al*. [9] significantly adds to the literature in describing NHL in India, and provides important material when studying the etiology of lymphoma on a global scale. As discussed above, the distribution of lymphoma subtypes in this hospital-based analysis differs markedly from those in Western countries, and although more similar to other Asian countries, is distinct. This study [9] further highlights the importance of analytic epidemiologic research in Asia to confirm recent findings from studies of Western populations in a population with distinctly different genetics and lifestyles, and to make new observations about the risk of lymphoma in Asia.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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