

To the editor:

## Population-based study on the impact of the familial form of Waldenström macroglobulinemia on overall survival

Waldenström macroglobulinemia (WM) is a chronic lymphoproliferative disorder (LP) characterized by an immunoglobulin M monoclonal gammopathy in the presence of lymphoplasmacytic lymphoma (LPL) in the bone marrow.<sup>1</sup> We have previously shown in a large population-based study that first-degree relatives of LPL/WM patients had an increased risk of developing LPs.<sup>2</sup>

An earlier single-center study on 257 WM patients showed that patients with a family history of WM or other B-cell disorders had a higher bone marrow involvement and were diagnosed at a younger age.<sup>3</sup> Furthermore, WM patients with a family history of a B-cell malignancy (n = 135) had worse response and shorter progression-free survival when treated with rituximab, compared with patients with sporadic WM. However, patients with familial WM had better response to bortezomib-containing therapy.<sup>4</sup>

Through nationwide Swedish registries and a national hematology/oncology network, we identified 2185 LPL/WM patients diagnosed between 1958 and 2007 and their 6460 first-degree relatives. Our nationwide study is the first, to our knowledge, to estimate the impact of having a family history of B-cell malignancy on overall survival in LPL/WM patients. Family history of any LP was defined as having a first-degree relative with LPL/WM, Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, chronic lymphocytic leukemia, and/or monoclonal gammopathy of undetermined significance. Overall survival was fitted with the Cox proportional hazard model to obtain hazard ratios (HRs) and 95% confidence intervals (95% CIs), adjusting for sex, age at diagnosis, and year of diagnosis (Table 1).

Overall, LPL/WM patients with a family history of any LP had an increased risk of death compared with sporadic LPL/WM patients (HR = 1.34; 95% CI, 1.03-1.75). The HR for each additive relative diagnosed with any LP was 1.22 (95% CI, 0.99-1.50). Survival differences have not been reported before in familial vs sporadic WM, but these findings are consistent with the earlier single-center study on

WM showing worse outcome in familial WM when treated with rituximab.<sup>4</sup> They are, however, in contrast to studies on Hodgkin lymphoma, non-Hodgkin lymphoma, and chronic lymphocytic leukemia in which familiarity was not associated with a poorer outcome.<sup>5-7</sup>

Of individual diseases, with the exception of Hodgkin lymphoma (with only 4 patients), family history of the other LPs showed a nonsignificant trend to increased risk. Female gender was associated with improved survival, which is consistent with earlier findings<sup>8</sup> and might be attributable to different clinical staging at diagnosis, comorbidity, and different distribution of prognostic factors. We performed several sensitivity analyses such as running the model on age and year-of-diagnosis scales to obtain HR for family history of any LP (HR = 1.32; 95% CI, 1.02-1.72 and HR = 1.31; 95% CI, 1.01-1.71, respectively). Furthermore, we matched each LPL/WM patient with family history and 4 sporadic patients, matched by age, gender, and year of diagnosis, and then did the same analysis with 10 matched sporadic patients. In addition, we performed cause-specific analyses, using WM death as outcome. The results from these analyses were similar to the main results (data not shown).

Our study has several strengths, for example, the generalizability of nationwide Swedish data and a hard end point (overall survival). Thorough sensitivity analyses were performed to rule out bias attributable to age and calendar period of diagnosis with essentially the same results as in the main analysis. Limitations include that as the follow-up time is through 2007, most patients did not receive novel agents, such as bortezomib, which might alleviate the negative prognostic value of familial disease.<sup>4</sup> Additionally, because of the design of the study, we did not have detailed clinical information such as bone marrow results, laboratory data, and treatment.

In summary, we have shown in this large population-based study on LPL/WM patients that family history of any LP was associated with a significantly poorer survival. These results support the theory that genetic susceptibility predisposes patients to a more severe form of LPL/WM. We recommend that family history of LPL/WM should be incorporated in the clinical workup of LPL/WM patients; however, until we gain more insight regarding the potential differences in genetic background, response to therapy, and rate of complications, clinical management should not differ between familial and sporadic LPL/WM patients.

**Table 1. Risk of death in LPL/WM patients in relation to family history of LPs**

	No. of patients	HR*	95% CI
<b>Family history of</b>			
Any LP	93	1.34	1.03-1.75
Per increasing number of relatives†		1.22	0.99-1.50
Multiple myeloma	13	1.47	0.76-2.85
Non-Hodgkin lymphoma‡	44	1.43	1.00-2.06
Hodgkin lymphoma	4	0.51	0.13-2.03
Chronic lymphocytic leukemia	17	1.43	0.71-2.88
LPL/WM	16	1.28	0.69-2.39
Monoclonal gammopathy of undetermined significance	11	1.12	0.53-2.37
Any LP (age scale)		1.32	1.02-1.72
Any LP (year-of-diagnosis scale)		1.31	1.01-1.71
Age at diagnosis (per 1-year increase)		1.06	1.05-1.07
Female gender		0.72	0.65-0.79
Year of diagnosis (per 1-year increase)		0.99	0.98-1.00

\*Cox model adjusted for age at diagnosis, gender, and year of diagnosis.

†The additive risk of each first-degree family member diagnosed with an LP.

‡Family members with non-Hodgkin lymphoma, excluding those with LPL/WM.

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**Contribution:** V.S., S.H.L., and S.Y.K. designed the study. S.Y.K., O.L., and I.T. obtained data. V.S. and S.H.L. performed the analyses. V.S. and S.Y.K. wrote the report. All the authors were involved in the analyses and the interpretation of the results. All authors read, gave comments, and approved the final version of the manuscript. All the authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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## References

1. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood*. 2011;117(19):5019-5032.
2. Kristinsson SY, Björkholm M, Goldin LR, McMaster ML, Turesson I, Landgren O. Risk of lymphoproliferative disorders among first-degree relatives of lymphoplasmacytic lymphoma/Waldenström macroglobulinemia patients: a population-based study in Sweden. *Blood*. 2008;112(8):3052-3056.
3. Treon SP, Hunter ZR, Aggarwal A, et al. Characterization of familial Waldenström's macroglobulinemia. *Ann Oncol*. 2006;17(3):488-494.
4. Treon SP, Tripsas C, Hanzis C, et al. Familial disease predisposition impacts treatment outcome in patients with Waldenström macroglobulinemia. *Clin Lymphoma Myeloma Leuk*. 2012;12(6):433-437.
5. Anderson LA, Pfeiffer RM, Rapkin JS, et al. Survival patterns among lymphoma patients with a family history of lymphoma. *J Clin Oncol*. 2008;26(30):4958-4965.
6. Ji J, Försti A, Sundquist J, Lenner P, Hemminki K. Survival in non-Hodgkin's lymphoma by histology and family history. *J Cancer Res Clin Oncol*. 2009;135(12):1711-1716.
7. Mauro FR, Giammartini E, Gentile M, et al. Clinical features and outcome of familial chronic lymphocytic leukemia. *Haematologica*. 2006;91(8):1117-1120.
8. Kristinsson SY, Eloranta S, Dickman PW, et al. Patterns of survival in lymphoplasmacytic lymphoma/Waldenström macroglobulinemia: a population-based study of 1,555 patients diagnosed in Sweden from 1980 to 2005. *Am J Hematol*. 2013;88(1):60-65.

## To the editor:

### A roadmap for discovery and translation in lymphoma

Non-Hodgkin lymphomas, Hodgkin lymphoma, and chronic lymphocytic leukemia comprise more than 80 unique subtypes<sup>1</sup> that can be further divided based on histology, immunophenotype, genetics, and other aspects of biology. Despite this diversity, advances in the treatment of lymphoma have served as models for curative cancer therapy.<sup>2-5</sup> To review the state of science in lymphoma biology, the American Society of Hematology (ASH) organized the inaugural ASH Meeting on Lymphoma Biology in August 2014. The Steering Committee for the meeting was asked to develop a roadmap for future discovery in lymphoma biology that could inform funding allocations (eg, requests for applications at the National Institutes of Health) and direct advocacy by ASH and other organizations. This roadmap is outlined in Table 1 and consists of both infrastructure and research priorities.

The investigation of individual lymphoma subtypes is largely limited by the same considerations that affect many other tumors, including:

- inadequate numbers of representative cell lines and in vivo models, including patient-derived xenografts and genetically engineered mouse models;
- inadequate characterization of the genetic, epigenetic, transcriptional, proteomic, and metabolomic landscape of each subtype;
- limited interest from pharma in rare subtypes with poorly understood pathobiology; and
- insufficient collaboration across centers, which limits both expertise and resource availability.

These inadequacies are compounded by the biologic heterogeneity within each lymphoma subtype. Preclinical studies that capture this heterogeneity will require large numbers of samples and/or models to facilitate patient stratification and biomarker validation. For most lymphoma subtypes, the necessary reagents to perform these studies either do not exist or are scattered across multiple institutions. As a result, many

patients with lymphoma continue to experience poor outcomes. These include patients with mantle cell lymphoma, subtypes of peripheral T-cell lymphoma, and lymphomas that harbor specific genetic markers [eg, del(17p) in chronic lymphocytic leukemia, concurrent *MYC* and *BCL2* translocations in diffuse large B-cell lymphoma].

The biological consequences of most genetic aberrations observed in human lymphomas remain unclear. Therefore, functional approaches are needed to distinguish driver events and to define critical dependencies that can be exploited therapeutically. Another high priority is to develop new prognostic models that incorporate biologically informative predictive factors along with clinical factors to enable patient selection for clinical trials and to highlight the biological pathways and mechanisms that influence therapeutic response. Comprehensive investigations of larger collections of clinically annotated patient samples are needed to identify additional determinants of treatment response, and these predictive features will inevitably shift with new therapies.

Advances in the targeting of lymphoma depend on an improved understanding of the fundamental biology of lymphoid development. Because the majority of B-cell lymphomas arise from cells undergoing the germinal center reaction, insights into this process shed light directly on lymphomagenesis. Lymphomas hijack other aspects of lymphocyte biology, including mechanisms that regulate proliferation, differentiation, interaction with immune and stromal cells in the microenvironment, motility, dissemination, and response to antigens. An important goal of future research will be to define genetic and nongenetic mechanisms that perturb these processes.

Interactions between lymphoma cells and nonmalignant cells within the bone marrow, lymph node, and other tumor microenvironments may represent additional targetable dependencies. Strategies to identify and therapeutically modulate these interactions are a priority, and include interventions to disrupt tumor angiogenesis, block critical adhesion molecules, and abrogate the nurturing effect