Elevated risk of chronic lymphocytic leukemia and other indolent non-Hodgkin's lymphomas among relatives of patients with chronic lymphocytic leukemia

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ABSTRACT

Background

Previous studies have shown increased familial risk for chronic lymphocytic leukemia. In the most comprehensive study to date, we evaluated risk of chronic lymphocytic leukemia and lymphoproliferative disorders among first-degree relatives of chronic lymphocytic leukemia cases compared to first-degree relatives of controls.

Design and Methods

Population-based registry data from Sweden were used to evaluate outcomes in 26,947 first-degree relatives of 9,717 chronic lymphocytic leukemia patients (diagnosed 1958-2004) compared with 107,223 first-degree relatives of 38,159 matched controls. Using a marginal survival model, we calculated relative risks (RR) and 95% confidence intervals as measures of familial aggregation.

Results

Compared to relatives of controls, relatives of chronic lymphocytic leukemia patients had an increased risk for chronic lymphocytic leukemia (RR=8.5, 6.1-11.7) and other non-Hodgkin's lymphomas (NHLs) (RR=1.9, 1.5-2.3). Evaluating NHL subtypes, we found a striking excess of indolent B-cell NHL, specifically lymphoplasmacytic lymphoma/Waldenström macroglobulinemia and hairy cell leukemia. No excesses of aggressive B-cell or T-cell lymphomas were found. There was no statistical excess of Hodgkin's lymphoma, multiple myeloma, or the precursor condition, monoclonal gammopathy of undetermined significance, among chronic lymphocytic leukemia relatives.

Conclusions

These familial aggregations are striking and provide novel clues to research designed to uncover early pathogenetic mechanisms in chronic lymphocytic leukemia including studies to identify germ line susceptibility genes. However, clinicians should counsel their chronic lymphocytic leukemia patients emphasizing that because the baseline population risks are low, the absolute risk for a first-degree relative to develop chronic lymphocytic leukemia or another indolent lymphoma is low. At this time, an increased medical surveillance of first-degree relatives of chronic lymphocytic leukemia patients has no role outside research studies.

Key words: chronic lymphocytic leukemia, non-Hodgkin's lymphoma, familial risk.

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Introduction

Chronic lymphocytic leukemia (CLL) is a malignancy characterized by the accumulation of small, mature-appearing lymphocytes in the bone marrow, blood, and lymphoid tissues. It is estimated that in 2008, CLL will account for 34% of all leukemias in the United States.[1] Known risk factors for disease are male gender, advanced age, white ancestry, and family history of hematologic malignancy.[2]

Using population-based data from Scandinavia, we previously showed that CLL, non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL) aggregated in families.[3-5] The risk for CLL was significantly elevated (7.5 fold) in relatives of CLL patients compared to relatives of controls consistent with the high risk seen in the Utah population.[6,7] We recently assembled a population-based cohort of lymphoplasmacytic lymphoma (LPL) and Waldenström macroglobulinemia (WM) patients in Sweden. Among relatives of these patients, we found an increased risk for CLL in addition to other LPL/WM and other lymphoma subtypes compared to relatives of controls.[8]

Familiality of CLL is also supported by case-control studies and studies of high-risk families.[9] Among high-risk CLL families that we have accrued in our clinical program,[10] relatives with other lymphomas including NHL and WM have been observed.[11] All of these studies support the role of germline genes underlying risk of CLL and related malignancies. Regions of the genome likely to contain susceptibility genes have been identified from linkage studies in high-risk families.[12] Specific genes have been implicated from candidate gene studies[13] and one genome-wide association study.[14] However, specific mutations causing susceptibility have not been identified.

To better define patterns of lymphoproliferative malignancies among close family members of CLL patients, and with the overall goal to provide clinicians with meaningful information to counsel CLL patients about familial risks for CLL and related malignancies, we have now extended our previous Swedish CLL registry study[3] substantially. Our present study includes nearly twice the number of first-degree relatives of cases as before. Using this very large population-based database, we were able to evaluate familial risk for CLL and for the first time, for specific NHL subtypes. In addition, using a nationwide cohort of patients with monoclonal gammopathy of uncertain significance (MGUS), we assessed the risk of MGUS among relatives of CLL patients. Beyond direct clinical implications of our present study, it also provides important clues of relevance to future research studies designed to uncover the role of predisposition genes in CLL and other hematologic tumors.

Design and Methods

Patients, controls, and relatives

The population-based data we used has been described previously.[15] In brief, we obtained all CLL patients (ICD7 code=2041), reported to the Swedish Cancer Registry diagnosed in 1958-2004. We selected individuals with CLL as a first, second or third primary tumor. For each patient, 4 population-based controls (matched by sex, year of birth, and county of residence) were selected from the Swedish Population database. Controls had to be alive and with no previous cancer at the date of diagnosis of the case. From the Swedish Multigenerational Registry, which includes information on parent-offspring relations for all Swedish citizens who were born 1932 or later, and living as residents of Sweden in 1961 or later, we obtained information on all first-degree relatives (parents, siblings, and offspring) of patients and controls. Approximately two-thirds of the cases and controls had relatives that could be linked to them.

The main reason for lack of linkable relatives was year of birth before 1932. Patients and controls with no linkable relatives were removed from the study. Patients, controls, and relatives were linked to the cancer registry to obtain all cancer outcomes (up to 3 cancer registrations). In an independent study, we also created a cohort of MGUS patients from a national network of hematology-oncology clinics in Sweden.[8] From this source, we obtained MGUS outcomes in cases, controls, and relatives.

Since NHL consists of a heterogeneous group of lymphomas, we used available ICD10 and SNOMED codes to classify NHL outcomes according to WHO definitions.[16] The Swedish registry codes are based on the Kiel classification[17] and it is not possible to define all of the current WHO NHLs based on the Swedish codes. However, WHO provides synonymous definitions across classifications and we used those translations whenever possible. Classification was possible mainly for the more recently diagnosed cases (1974 and later). Because the numbers of specific NHLs were sometimes small, we also grouped them into larger categories including all B-cell, all T-cell, indolent, and aggressive similar to strategies in other population-based analyses.[18] We were also able to obtain more complete assessment of LPL/WM in relatives by linking them to our recently created cohort of LPL/WM patients.[8] This cohort was assembled from outpatient hematology clinics, Inpatient Hospital Registry (IHR), and Cancer Registry. WM patients from clinics and the IHR were included since we have previously shown that although the diagnostic accuracy of WM is very high, it is underreported to the Cancer Registry,[19] probably due to the indolent disease course of many patients.

Statistical methods

The analytic method has been described previously.[3,20] We classified relatives as *affected* if they had a primary cancer registration with the tumor of interest. We model the age at censoring or age at onset of disease in a relative of a proband by a marginal proportional hazards model. Familial aggregation for each condition is evaluated by testing the hazard ratio of being a relative of a case compared with being a relative to a control. The model was fitted using the PHREG procedure in SAS v9.1. Relative risk (RR) is used to denote the hazard ratio

defined above, with 95% confidence intervals (CI). Since every case is a proband, families with more than one case appear twice in the dataset. The robust sandwich covariance matrix accounts for these dependencies. We tested separately for increased risk for CLL, NHL, HL, myeloma (MM), and MGUS in relatives, as well as *any lymphoproliferative (LP) cancer*. Sex was included as a covariate in the model. We also stratified the analyses by gender, type of relative, and early (≤65) versus late (>65) age at onset of CLL in the proband. We also computed relative risks for subtypes of NHL in relatives as described above. Since NHL subtypes were available starting only in 1974, we restricted the time period to 1974 and later for risk calculations.

Results

We identified all (n=9,717) CLL patients from the Swedish Cancer Registry with linkable first-degree relatives. The distribution of sex, age at diagnosis, and calendar year of diagnosis is shown in Table 1. The predominance of males is consistent with higher incidence rates in males. The mean age at diagnosis was 68 years which is slightly younger than in the total sample of CLL patients (mean age 70 years) and reflects the fact that more of the older patients in the registry did not have linkable relatives. Two-thirds of the cases were diagnosed in 1985 or later.

The numbers of total relatives, their average age at observation, as well as the numbers in each stratum are shown in Table 2 along with the numbers of cases of CLL. The table shows that the case and control relatives have similar characteristics in terms of the proportions of relatives by gender, age at censoring of relatives, and type of relative. Figure 1 shows the differences in age at diagnosis of CLL between relatives of cases compared to controls by generation. The figure shows that among parent-offspring pairs with CLL, the parents had an older age at diagnosis than the offspring (71.5 *vs.* 55.5, $p<0.0001$),which is consistent with the anticipation hypothesis. However the age at diagnosis of CLL did not differ between offspring of cases compared to offspring of controls (55.5 *vs.* 57.4, ns). In fact, age at diagnosis did not differ between parents of cases versus parents of controls or siblings of cases versus siblings of controls. These patterns suggest the parent-offspring difference is due to the difference in follow-up time between parent and offspring generations.

Table 3 shows the risks for CLL and lymphoproliferative disorders comparing first-degree relatives of CLL patients to first-degree relatives of controls. Consistent with our previous report, the relative risk of CLL was extremely high in the total sample (RR=8.5, 95%CI=6.1-11.7) and in each stratum. NHL (excluding CLL) was also significantly elevated in relatives of CLL patients. The risks of HL and MGUS were elevated but not statistically significant. The risk of MM was not increased among relatives of CLL cases. The stratified analyses showed no differences by sex, age at diagnosis of proband, or type of relative, although MM risk was elevated in offspring.

As shown in Table 4, familial risk for NHLs varied by specific lymphomas. Approximately 45% of NHL cases could be classified into subtypes. We tested all B-cell and all T-cell NHLs but the small number of T-cell NHL patients precluded further breakdown. Within B-cell NHLs, all indolent and aggressive NHLs were tested. We further classified indolent NHL subtypes into follicular lymphoma, nodal marginal zone lymphoma, mantle cell lymphoma, hairy cell leukemia, and LPL/WM.

Table 1. Characteristics of patients with chronic lymphocytic leukemia and controls.

Variable	CLL patients	Controls
Total number, N. (%)	9,717 (100)	38,159 (100)
Males, N. (%)	6,185 (64)	24,427 (64)
Females, N. (%)	3,532 (36)	13,732 (36)
Age at diagnosis (yrs), mean (s.d.)	68.1 (11.2)	
Number of patients by age (yrs), N. (%)		
<40	115 (1)	
40-65	3584 (37)	
>65	6018 (62)	
Year of diagnosis, N. (%)		
1958-1974	1284 (13)	
1975-1984	1946 (20)	
1985-1994	2752 (28)	
1995-2004	3735 (39)	

Table 2. Characteristics of first-degree relatives of patients with chronic lymphocytic leukemia and controls.

	Relatives of CLL patients			Relatives of controls		
Variable	N. total (%)	Mean age (sd)	N. CLL cases	N. total (%)	Mean age (sd)	N. CLL cases
All	26,947(100)	54.4 (15.7)	159	107,223 (100)	54.5 (15.9)	76
Males	13,891 (50)	54.1 (15.2)	98	55,744 (51)	54.2 (15.5)	40
Females	13,658 (50)	54.8 (16.2)	61	53,980 (49)	54.8 (16.2)	36
Probands age dx ≤65	13,691 (50)	55.0 (11.7)	104	54,902 (50)	53.9 (19.2)	53
Probands age dx >65	13,658 (50)	55.2 (11.7)	55	54,822 (50)	53.7 (19.0)	23
Parents	3,202 (12)	79.0 (10.6)	68	12,968 (12)	79.2 (10.7)	36
Siblings	2,560 (10)	57.8 (10.0)	26	10,386 (10)	57.9 (9.8)	12
Offspring	21,185 (78)	50.3 (13.2)	65	83,869 (78)	50.1 (13.3)	28

Table 3. Risks of lymphoproliferative tumors among relatives of patients with chronic lymphocytic leukemia versus relatives of controls.[1]

Outcome	Number of relatives affected		All first-degree relatives	Male relatives	Female relatives	Case age at dx ≤65	Case age at dx >65	Parents	Siblings	Offspring
	CLL patients	Controls								
CLL	159	76	**8.5 (6.1-11.7)**	**9.9 (6.8-14.3)**	**6.7 (4.4-10.2)**	**7.9 (5.7-11.0)**	**9.5 (5.8-15.4)**	**7.8 (5.2-11.7)**	**8.8 (4.4-17.5)**	**9.2 (5.9-14.4)**
NHL	131	278	**1.9 (1.5-2.3)**	**1.8(1.4-2.4)**	**2.0 (1.5-2.7)**	**1.8 (1.3-2.4)**	**2.0 (1.5-2.7)**	**1.9 (1.3-2.8)**	**2.0 (1.1-3.7)**	**1.9 (1.4-2.4)**
HL	28	75	1.5 (0.96-2.3)	1.5 (0.86-2.6)	1.4 (0.72-2.9)	1.4 (0.74-2.5)	1.6 (0.87-3.0)	1.2 (0.41-3.8)	1.6 (0.51-5.2)	1.5 (0.91-2.5)
MM	38	124	1.2 (0.85-1.8)	1.1 (0.67-1.98)	1.3 (0.78-2.1)	1.0 (0.61-1.7)	1.5 (0.90-2.6)	0.92 (0.54-1.6)	0.81 (0.2-3.7)	**1.8 (1.1-3.0)**
MGUS	25	71	1.4 (0.88-2.2)	1.1 (0.56-2.3)	1.6 (0.90-3.0)	0.67 (0.28-1.6)	**2.1 (1.2-3.7)**	1.2 (0.41-3.8)	0.73 (0.2-3.3)	1.6 (0.94-2.7)
Any LP	356	553	**2.6 (2.2-3.0)**	**2.7 (2.2-3.3)**	**2.5 (2.0-3.0)**	**2.6 (2.1-3.2)**	**2.6 (2.1-3.2)**	**2.6 (2.1-3.3)**	**3.0 (2.0-4.6)**	**2.5 (2.1-3.0)**

[1]*Hazard ratios and 95% confidence intervals. Bold entries indicate statistically significant results (p<0.05).*

Table 4. Relative risks for specific non-Hodgkin's lymphoma subtypes.[1]

Outcome	Number of relatives affected		RR[2]
	CLL patients	Controls	
B-cell NHLs	58	127	**1.8 (1.3-2.5)**
Indolent B-cell NHL	39	73	**2.2 (1.5-3.2)**
Follicular lymphoma	16	42	1.6 (0.87-2.8)
Nodal marginal zone lymphoma	0	3	–
Mantle cell lymphoma	2	7	1.1 (0.24-5.5)
Hairy cell leukemia	5	6	**3.3 (1.0-10.9)**
LPL/WM	16	16	**4.0 (2.0-8.2)**
Aggressive B-cell NHL	6	24	1.0 (0.41-2.5)
T-cell NHLs	3	9	1.3 (0.36-4.9)

[1]*Based on the most recent WHO[16] lymphoma classification nomenclature, the category "indolent B-cell lymphoma" includes: follicular lymphomas (centroblastic and centrocytic follicular lymphomas); nodal marginal zone lymphoma (monocytoid B-cell lymphoma); mantle cell lymphoma (centrocytic lymphoma); hairy cell leukemia; and lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia (including immunocytoma). The category "aggressive B-cell lymphoma" includes: diffuse large B-cell lymphoma (including immunoblastic B-cell lymphoma, anaplastic large B-cell lymphoma, centroblastic diffuse lymphoma, and Burkitt's lymphoma. The category "T-cell lymphoma" includes: mycosis fungoides, Sezary syndrome, peripheral T-cell lymphomas (including anaplastic T-cell lymphoma). [2]Hazard ratios and 95% confidence intervals denote measures of relative risks (RRs). Bold entries indicate statically significant results (p<0.05).*

Within the aggressive B-cell NHL category, we included diffuse large B-cell lymphoma (DLBCL) and Burkitt's lymphoma although there were no cases of Burkitt's lymphoma in either case or control relatives. We found that B-cell NHL aggregated significantly in relatives of CLL patients, but T-cell NHL did not. Within the B-cell NHL category, indolent NHL subtypes as a whole aggregated significantly while the major aggressive NHL subtype, DLBCL did not aggregate in CLL relatives. Among the indolent NHL subtypes, there was also a striking overall 4-fold increased risk of LPL/WM in relatives of CLL patients. When we tested LPL and WM separately, each showed significant aggregation (*data not shown*). Hairy cell leukemia was also significantly increased among case relatives although the numbers were small. Follicular lymphoma risk was non-significantly increased among case relatives. There were no cases of nodal marginal zone lymphoma among relatives of CLL patients. The risk of mantle cell lymphoma was not elevated but the numbers were small.

Discussion

This comprehensive population-based study, including almost 10,000 CLL patients and their close to 27,000 first-degree relatives, and a more complete ascertainment of MGUS and subtypes of NHL, increases our understanding of the familial relationships among lymphoproliferative tumors and precursors. We detected a very strong aggregation specific to CLL (consistent with our earlier study[3] and others in the literature)[6,7] but also found increased risk of other NHLs among relatives, limited to indolent B-cell NHLs. We observed a strong aggregation of LPL/WM in CLL families consistent with our study of relatives of LPL/WM cases.[8] This finding is in accordance with a study showing similar gene expression patterns in WM and CLL.[21] We found aggregation of hairy cell leukemia in CLL families which is a novel observation. However, one of the more common indolent lymphomas, follicular lymphoma, did not aggregate significantly in relatives of CLL cases. T-cell lymphomas and diffuse large cell lymphomas also did not aggregate in relatives. HL was associated with CLL in our earlier smaller study.[3] In the present expanded study, the RR was 1.5 (and within the 95% confidence interval of the previous study) but did not reach statistical significance (p=0.07). This difference may be due to our current study having a much larger sample size. The risk for MGUS was elevated but was not significant. MGUS is a heterogeneous condition and it is possible that there is familial aggregation with CLL specific to certain Ig classes. However, lack of information on the Ig class made this impossible to evaluate. The relative risk for MM was not elevated among case relatives.

Genetic anticipation is a term that refers to an earlier age at onset or increasing severity of a disease in successive generations. Trinucleotide repeat expansions explain the phenomenon of anticipation in some Mendelian neurodegenerative diseases such as Huntington's disease, myotonic dystrophy, and spinocerebellar ataxia.[22] Epigenetic changes and abnormalities in telomeres have also been suggested as possible mechanisms that may contribute to anticipation in some diseases.[23] Anticipation has been widely investigated in complex diseases but findings are often uncertain given the well described truncation bias involved in family studies, where the offspring generation is not followed

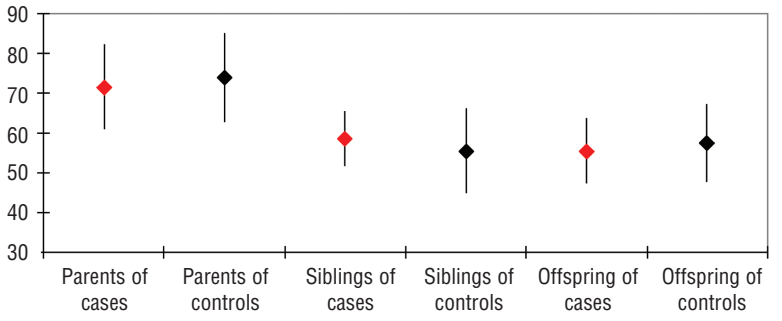

Figure 1. Age at diagnosis of chronic lymphocytic leukemia (Mean and SD) among relatives of cases (red) and relatives of controls (black) stratified by relative type.

up as long as the parent generation.[24,25] This potential bias is shown in Figure 1 where among familial CLL cases, offspring were diagnosed with CLL at an earlier age than the parent group. However, offspring of controls with CLL had a similar age at diagnosis as offspring of cases indicating that this difference is likely due to differences in follow-up time between generations and not explained by earlier diagnosis in children of parents with CLL. This is consistent with our earlier studies showing no anticipation after correcting for bias in follow-up times.[3,26]

It is important to consider the clinical implications of our findings. Compared to relatives of controls, first-degree relatives of CLL patients have an 8.5- fold relative risk for developing CLL and are also at an increased risk for developing other indolent forms of NHL. Relatives are at 2.6-fold relative risk for developing any lymphoproliferative tumor. However, because the baseline risk of these conditions in the population is low, the absolute risk of a relative of a CLL patient developing CLL or a related malignancy is still very low. The National Cancer Institute SEER program estimates the lifetime risk of CLL to be about 0.46% and that of other NHLs as a group to be 2.05%.[1] We have shown that the increased risk of NHL is limited to indolent B-cell subtypes. Morton *et al.*[18] have tabulated the breakdown of the case numbers of all subtypes of lymphoid malignancies from the SEER registries from 2001-2003. From these data, all of the indolent B-cell NHLs (not including myeloma or CLL) comprise about one half of all NHLs.

One can still question whether there is an advantage in prevention or early detection for a relative knowing that they are at increased risk for CLL. Currently, early detection of CLL is not likely to affect outcome since stage 0 CLL is usually not treated. This is also true for other indolent lymphomas since they are generally not treated in the early stages. Relatives of CLL cases from high-risk families (i.e. families with at least 2 cases of CLL) are at increased risk for having a precursor clone, monoclonal B-cell lymphocytosis (MBL) which is detected by immunophenotyping.[27-29] We did not have information about MBL in our registry study so we could not evaluate the general risk of MBL among relatives of CLL cases. However, the transformation rate from MBL to CLL requiring therapy is only about 1% per year[30,31] and has been shown to depend on the level of lymphocytosis seen at diagnosis.[31,32] These characteristics of CLL make it quite different from other common solid tumors where early detection of the tumor or precursor can affect survival. For example, relatives of patients with colon cancer are at increased risk for developing colon cancer. Consequently, they are advised to be screened for colon cancer at an earlier age and more frequently than individuals at average risk in order to detect tumors or pre-cancerous lesions at a treatable stage.[33] In contrast, while relatives of patients with CLL can be informed that they are at higher relative risk for CLL and related lymphomas (compared to family members of unaffected individuals), it should be emphasized that the absolute risk for developing CLL and other hematologic malignancies is very low, there is no treatment for early lesions, and thus no increased medical surveillance is necessary at this time. One exception to this conclusion may be the need to screen for MBL/CLL in a first-degree relative of a CLL patient who is a potential stem cell donor.[34] Of importance for future studies designed to uncover susceptibility genes in CLL, for the first time, we evaluated patterns of various lymphoma subtypes among family members of CLL patients and found increased risk for some indolent NHLs. Simultaneously, we did not find risk of aggressive B-cell or T-cell lymphomas to be statically elevated among family members of CLL patients. Neither was there any excess of HL, MM, or the precursor condition MGUS among CLL relatives. Thus, our findings support a role for germline genes specific to CLL (given the high familial risk for CLL alone) and genes shared by CLL and indolent lymphomas. An alternate explanation is that the same genes are involved but lead to higher risk for CLL than other lymphomas. At this time, germline gene mutations have not been identified from linkage studies of large numbers of families making it likely that multiple genes with smaller effects contribute to susceptibility.[12] In fact, a recent whole genome association study has identified a few novel gene regions associated with CLL susceptibility.[14] Familial aggregation could also, at least in part, be a result of shared environment. Although there are no strongly associated exogenous risk factors for CLL, there is evidence for exposure to a common antigen among CLL cases.[2,35] It is unclear if these are auto-antigens or antigens from pathogenic microorganisms. The challenge will be both to identify

critical environmental or infectious factors in CLL, host genetic factors and determine how they interact in the pathway to CLL.

Our study has several strengths, including its large size as well as the application of high-quality data from Sweden in a stable population with access to standardized universal medical health care during the entire study period. The use of the nationwide register-based case-control design ruled out recall-bias and ensured a population-based setting. We recently conducted a nationwide validation study of lymphoproliferative malignancies, including 202 CLL cases diagnosed in Sweden 1964-2003.[19] In that study, we found a 98% diagnostic accuracy of the Registry. However, we found a rate of approximately 12% underreporting of CLL cases from the hospitals to the Swedish Cancer registry. When we assessed these findings in further detail, we observed the underreporting of CLL to be very constant over all calendar periods. As expected, elderly CLL patients and individuals with more indolent disease were more common in the underreported category. However, the level of underreporting of CLL should be similar in case and control relatives and not lead to bias. Our study has other limitations. We did not have detailed clinical or laboratory data on cases or relatives. It is possible that subtypes of CLL (based on cytogenetics, mutation status, ZAP70, protein expression, gene expression profile, or other factors) show different familial risk patterns. We were not able to evaluate the familial aggregation of MBL with CLL in this population. Finally, our study is limited to one population so the findings may not be applicable to other groups.

In conclusion, we found elevated risk of CLL and related indolent NHLs among first-degree relatives of CLL patients, which supports a role for germ line susceptibility genes, possibly interacting with environmental factors. Clinicians need to keep in mind the low baseline risk of CLL in the general population. When counseling CLL patients about practical implications of the observed 8.5-fold excess relative risks of CLL and the increased risk of related indolent lymphomas among relatives to CLL patients, it must be stressed that the absolute risk for a first-degree relative to develop CLL or another indolent lymphoma is still very low. Based on current clinical knowledge, at this time, an increased medical surveillance of first-degree relatives of CLL patients has no role outside research studies.

Authorship and Disclosures

LRG, OL, SYK, MB and IT designed the study and obtained data. LRG analyzed data. All the authors were involved in the interpretation of the results. LRG and OL wrote the paper. 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.

The authors reported no potential conflicts of interest.

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