Second Malignancy Risks After Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia: Differences by Lymphoma Subtype

Lindsay M. Morton, Rochelle E. Curtis, Martha S. Linet, Elizabeth C. Bluhm, Margaret A. Tucker, Neil Caporaso, Lynn A.G. Ries, and Joseph F. Fraumeni Jr

From the Divisions of Cancer Epidemiology and Genetics, Rockville, MD, and of Cancer Control and Population Sciences, Bethesda, MD, National Cancer Institute, National Institutes of Health, Department of Health and Human Services; and Washington Hospital Center, Section of General Internal Medicine, Washington, DC.

Submitted March 7, 2010; accepted August 23, 2010; published online ahead of print at www.jco.org on October 12, 2010.

Supported by the Intramural Research Program of the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Lindsay M. Morton, PhD, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, 6120 Executive Blvd, EPS 7040, MSC#7238, Rockville, MD 20892; e-mail: mortonli@mail.nih.gov.

© 2010 by American Society of Clinical Oncology

0732-183X/10/2833-4935/\$20.00

DOI: 10.1200/JCO.2010.29.1112

A B S T R A C T

Purpose

Previous studies have shown increased risks of second malignancies after non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL); however, no earlier investigation has quantified differences in risk of new malignancy by lymphoma subtype.

Patients and Methods

We evaluated second cancer and leukemia risks among 43,145 1-year survivors of CLL/small lymphocytic lymphoma (SLL), diffuse large B-cell lymphoma (DLBCL), or follicular lymphoma (FL) from 11 Surveillance, Epidemiology, and End Results (SEER) population-based registries during 1992 to 2006.

Results

Among patients without HIV/AIDS-related lymphoma, lung cancer risks were significantly elevated after CLL/SLL and FL but not after DLBCL (standardized incidence ratio [SIR], CLL/SLL = 1.42, FL = 1.28, DLBCL = 1.00; Poisson regression P for difference among subtypes, $P_{\text{Diff}} = .001$). A similar pattern was observed for risk of cutaneous melanoma (SIR: CLL/SLL = 1.92, FL = 1.60, DLBCL = 1.06; $P_{\text{Diff}} = .004$). Acute nonlymphocytic leukemia risks were significantly elevated after FL and DLBCL, particularly among patients receiving initial chemotherapy, but not after CLL/SLL (SIR: CLL/SLL = 1.13, FL = 5.96, DLBCL = 4.96; $P_{\text{Diff}} < .001$). Patients with HIV/AIDS-related lymphoma ($n = 932$) were predominantly diagnosed with DLBCL and had significantly and substantially elevated risks for second anal cancer (SIR = 120.50) and Kaposi's sarcoma (SIR = 138.90).

Conclusion

Our findings suggest that differing immunologic alterations, treatments (eg, alkylating agent chemotherapy), genetic susceptibilities, and other risk factors (eg, viral infections, tobacco use) among lymphoma subtypes contribute to the patterns of second malignancy risk. Elucidating these patterns may provide etiologic clues to lymphoma as well as to the second malignancies.

J Clin Oncol 28:4935-4944. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Non-Hodgkin's lymphomas (NHLs) are closely related yet heterogeneous diseases distinguished by specific morphologic, immunophenotypic, genetic, and clinical features.¹ Some NHLs are potentially curable with chemotherapy and, less often, radiotherapy; however, treatment protocols vary by NHL subtype and continue to evolve.² In addition, the clinical course and survival after NHL diagnosis vary among subtypes, with the 5-year relative survival for the major NHL subtypes ranging from 52% for the aggressive diffuse, large B-cell lymphoma (DLBCL) to approximately 75% for the more indolent follicu-

lar lymphoma (FL) and chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).³ Evidence increasingly supports some etiologic heterogeneity among NHL subtypes as well, with particularly notable differences in risk for infectious agents, autoimmune diseases, and genetic susceptibility.⁴⁻⁹

Previous studies have shown increased risks of second malignancies after NHL¹⁰⁻²² and CLL,²³⁻³⁰ which are potentially related to chemotherapy and radiotherapy; underlying immune dysfunction; or shared risk factors, such as immunodeficiency, selected viral infections (eg, HIV), lifestyle factors (eg, tobacco), and genetic susceptibility. Although treatments, immunologic alterations, and risk factors

may vary by lymphoma subtype, no earlier investigation has quantified differences in risk of new malignancy by lymphoma subtype, which could provide important etiologic clues to lymphoma as well as to the second malignancies. Improving our understanding of second malignancy risks is also critical for the health of the rapidly growing population of cancer survivors. We therefore evaluated second malignancy risks among survivors of the major lymphoma subtypes (ie, CLL/SLL, DLBCL, and FL) reported to Surveillance, Epidemiology, and End Results (SEER) population-based cancer registries.

PATIENTS AND METHODS

Patients

SEER registries collect data on patient demographics, primary tumor site and morphology, first course of treatment (ie, radiotherapy, chemotherapy, immunotherapy, surgery), and follow-up for occurrence of new malignancies and vital status. Since 1990, 11 SEER registries representing approximately 13% of the US population (states of Connecticut, Hawaii, New Mexico, and Utah; metropolitan areas of Atlanta, GA; Detroit, MI; Seattle/Puget Sound, WA; and Los Angeles County, San Francisco/Oakland, and San Jose/Monterey, CA; and rural Georgia)³ also have collected data on HIV/AIDS status at NHL diagnosis (including SLL, DLBCL, and FL but not CLL). These data are estimated to identify accurately approximately 90% of patients with AIDS-related NHL.³¹⁻³² We assumed that all patients with CLL did not have HIV/AIDS-related disease.

This analysis included patients of all ages who survived for at least 1 year after diagnosis during 1992 to 2006 with first primary CLL/SLL, DLBCL, or FL, as reported to a SEER registry collecting HIV/AIDS data. Eligible patients were identified by using International Classification of Diseases for Oncology, third edition (ICD-O-3)³³ morphology codes (CLL/SLL: 9670, 9823; DLBCL: 9678 to 9680, 9684 [B-cell immunophenotype only]; FL: 9690 to 9691, 9695 to 9698).^{1,34} Together, these major subtypes include two thirds of all patients with NHL and CLL. For survivors of less common lymphomas, the rarity of specific second malignancies precluded calculation of stable risk estimates. We restricted the analysis to 1992 to 2006 to include SEER registries with HIV/AIDS data and to more accurately identify lymphoma subtypes, which have higher misclassification in earlier time periods because of changes in classification.³⁴

Second primary invasive cancers and leukemias that developed at least 1 year after initial lymphoma diagnosis were identified via SEER registry files. The SEER standard for case ascertainment is $\geq 98\%$. Subsequent NHLs and lymphocytic leukemias were excluded from overall second malignancy risk estimates because of the difficulty of distinguishing disease progression from independent primary cancers.

Statistical Analysis

Patients were observed from 1 year after diagnosis with first primary CLL/SLL, DLBCL, or FL until diagnosis with a second primary invasive cancer or leukemia, last follow-up, death, or end of the study (December 31, 2006), whichever occurred first. The first year of follow-up was excluded because of heightened medical screening after a patient's initial diagnosis, which may bias second malignancy ascertainment. In our cohort, 98.2% of patients were observed through 2006; 14,271 (33.1%) died, 28,105 (65.1%) were last known alive, and 769 (1.8%) were lost to follow-up. SEER actively traces patients for vital status (eg, linkage to state death certificate files and/or national databases, contact with treating physicians), regardless of emigration from a SEER area. However, SEER does not ascertain malignancies occurring in patients who moved out of registry areas, and dates of emigration are unknown. On the basis of 2000 census data, the 5-year emigration rate among adults age 40 years or older was 5.6% for the states in this analysis (ie, CA, CT, GA, HI, MI, NM, UT, and WA).³⁵

Comparisons with the general population. Standardized incidence ratios (SIRs) and exact 95% CIs were used to quantify second malignancy risks by comparing the observed (O) number of second malignancies with that ex-

pected (E) in the general population (SEER*Stat software, version 6.5.1; Surveillance Research Program, National Cancer Institute, Bethesda, MD). The expected number of malignancies was calculated by using data from the 11 SEER registries with HIV/AIDS data, stratifying by age (5-year groups), sex, ethnicity (white, black, other), and calendar year (1992 to 1995, 1996 to 1999, 2000 to 2003, 2004 to 2006). All analyses were stratified by HIV/AIDS status at lymphoma diagnosis. We also evaluated second malignancy risks after CLL and SLL separately, because these entities have only recently been recognized as the same disease.¹ Because second malignancy risks were generally similar after CLL and SLL (Appendix Table A1, online only), we present results for CLL/SLL combined.

Comparisons among lymphoma subtypes. For second primary malignancies with at least 10 observed occurrences after all three lymphoma subtypes, we directly assessed differences in second malignancy risks among lymphoma subtypes (P_{Diff}) by using a likelihood ratio test derived from multivariate Poisson regression analyses, which incorporated SEER registry general population rates (Epicure software, release 2.10; HiroSoft International, Seattle, WA) and which stratified by sex, age at lymphoma diagnosis, and latency. Additional stratification by ethnicity and calendar year did not materially affect results. For those second malignancies with a significant difference in risk ($P_{\text{Diff}} < .05$) by lymphoma subtype, we additionally examined SIRs by sex, age and calendar year of lymphoma diagnosis, latency, initial treatment, and second malignancy characteristics (eg, histology) to test differences in the SIRs for these variables within each lymphoma subtype by using multivariate Poisson regression models.

RESULTS

Study Population

Among the 42,213 patients without known HIV/AIDS at lymphoma diagnosis, those with CLL/SLL were older and were more likely to be men than those with DLBCL or FL (Table 1). Chemotherapy was received as a first course of therapy by at least 83% of patients with DLBCL, 55% with FL, and 29% with CLL/SLL. Initial radiotherapy was used to treat 34% of patients with DLBCL and 21% with FL, but it was rarely used for CLL/SLL (3%). Patients with HIV/AIDS-related lymphoma ($n = 932$) were predominantly men, younger, and diagnosed with DLBCL.

Second Malignancy Risks Among Patients Without Known HIV/AIDS

Among patients without known HIV/AIDS at lymphoma diagnosis, overall malignancy risk was significantly higher than expected in the general population after CLL/SLL ($O = 1,450$; $SIR = 1.19$; 95% CI, 1.13 to 1.25) and DLBCL ($O = 873$; $SIR = 1.11$; 95% CI, 1.04 to 1.19) but not after FL ($O = 685$; $SIR = 1.03$; 95% CI, 0.96 to 1.11; Table 2). Poisson regression analyses, which adjusted for age, sex, and follow-up time, confirmed that the overall second malignancy risk was significantly different among the lymphoma subtypes ($P_{\text{Diff}} < .001$; Table 2). However, the risk patterns differed substantially by specific second malignancy.

Of the nonhematologic second malignancies, risks for lung cancer and cutaneous melanoma were elevated after the more indolent lymphomas, CLL/SLL and FL, but not after the more aggressive DLBCL (lung $P_{\text{Diff}} = .001$, melanoma $P_{\text{Diff}} = .004$). Survivors of CLL/SLL were also more prone than the general population to develop salivary gland, colon, anal, and thyroid cancers, whereas deficits of pancreatic and breast cancers were limited to FL survivors. In contrast, observed numbers of nonhematologic second malignancies did not differ significantly from expectation after DLBCL.

Second Malignancies After NHL by NHL Subtype

Table 1. Selected Characteristics of 43,145 Patients Surviving at Least 1 Year After an Initial Diagnosis of CLL/SLL, DLBCL, or FL in 11 SEER Registries, 1992-2006

Characteristic by Patient Group	Diagnosis					
	CLL/SLL		DLBCL		FL	
	No.	%	No.	%	No.	%
Patients without known HIV/AIDS*						
Total	15,915	100.0	15,243	100.0	11,055	100.0
Age at first primary malignancy diagnosis, years						
0-40	274	1.7	2,265	14.9	858	7.8
40-49	1,175	7.4	1,972	12.9	1,784	16.1
50-59	2,839	17.9	2,768	18.2	2,658	24.0
60-69	4,235	26.6	3,181	20.9	2,517	22.8
70-79	4,750	29.8	3,379	22.2	2,294	20.8
≥ 80	2,642	16.6	1,678	11.0	944	8.5
Mean	67.2	—	59.3	—	60.2	—
Sex						
Male	9,244	58.1	7,975	52.3	5,484	49.6
Female	6,671	41.9	7,268	47.7	5,571	50.4
Ethnicity						
White	13,888	87.3	12,584	82.6	9,773	88.4
Black	1,170	7.4	994	6.5	517	4.7
Other/unknown	857	5.4	1,665	10.9	765	6.9
Year of first primary malignancy diagnosis						
1992-1995	4,448	27.9	3,467	22.7	2,722	24.6
1996-1999	4,224	26.5	4,140	27.2	3,030	27.4
2000-2003	4,805	30.2	4,953	32.5	3,468	31.4
2004-2006	2,438	15.3	2,683	17.6	1,835	16.6
First course of treatment						
Any radiation	490	3.1	5,114	33.5	2,375	21.5
No/unknown radiation	15,425	96.9	10,129	66.5	8,680	78.5
Any chemotherapy	4,680	29.4	12,698	83.3	6,149	55.6
No/unknown chemotherapy	11,235	70.6	2,545	16.7	4,906	44.4
Mean person-years at risk	4.3	—	4.1	—	4.6	—
Patients with known HIV/AIDS*						
Total	25	100.0	827	100.0	80	100.0
Mean age at first primary malignancy diagnosis, years	53.5	—	42.8	—	50.8	—
Sex						
Male	22	88.0	743	89.8	61	76.3
Female	3	12.0	84	10.2	19	23.8
Mean person-years at risk	3.1	—	3.5	—	4.2	—

Abbreviations: CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; SEER, Surveillance, Epidemiology, and End Results.

*HIV/AIDS status was coded directly from the medical record at the time of initial non-Hodgkin's lymphoma (ie, SLL, DLBCL, FL) diagnosis. SEER does not collect information on HIV/AIDS status for patients with CLL. We assumed that all patients with CLL did not have HIV/AIDS-related disease.

Of the hematologic second malignancies, risks for Hodgkin's lymphoma were elevated after all three lymphoma subtypes, but risks varied by lymphoma subtype ($P_{\text{Diff}} = .009$), with highest risks after CLL/SLL. Acute nonlymphocytic leukemia occurred excessively after DLBCL and FL but not CLL/SLL ($P_{\text{Diff}} < .001$), whereas chronic myeloid leukemia risk was elevated after DLBCL.

Lung cancer was the most common second malignancy to occur in excess, with increased risks limited to survivors of CLL/SLL (SIR = 1.44) and FL (SIR = 1.28). Patients diagnosed at younger ages (< 55 years) with CLL/SLL or FL were particularly prone to lung cancer (SIR: CLL/SLL = 2.32; FL = 2.01), with a downward trend in relative risk with increasing age after CLL/SLL ($P_{\text{Trend}} = .005$) and FL ($P_{\text{Trend}} = .01$; Table 3). Initial chemotherapy appeared to heighten lung cancer risk after CLL/SLL, but risks were elevated in all initial

treatment groups. Women had somewhat greater lung cancer risk than men after FL. In analyses by histologic type, lung cancer risk after both CLL/SLL and FL appeared higher for non-small-cell than small-cell lung carcinoma, but the risk differences were not significant (CLL/SLL, $P_{\text{homogeneity}} = .07$; FL, $P_{\text{homogeneity}} = .1$).

Risks for cutaneous melanoma followed a pattern similar to lung cancer, with excesses limited to the more indolent lymphomas (SIR: CLL/SLL = 1.92; FL = 1.60). The melanoma risk varied by age at CLL/SLL diagnosis, with greater than two-fold risks for patients diagnosed before age 70 years ($P_{\text{Trend}} = .02$; Table 4). The excess risk after CLL/SLL was pronounced for melanomas occurring on more heavily sun-exposed sites (SIR: face/head/neck = 2.24; limbs = 2.09) and for melanomas ≥ 1 mm thick (SIR: 1.0 to 3.9 mm = 2.57; ≥ 4.0 mm = 3.30). Variations in melanoma risk among FL survivors by age,

Table 2. Second Primary Malignancy Risks Among Patients Surviving at Least 1 Year After an Initial Diagnosis of CLL/SLL, DLBCL, or FL in 11 SEER Registries, 1992-2006

Malignancy Risk	Diagnosis									P Difference Among Lymphoma Subtypes*
	CLL/SLL			DLBCL			FL			
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	
Patients without known HIV/AIDS†										
All second primary malignancies‡	1,450	1.19§	1.13 to 1.25	873	1.11§	1.04 to 1.19	685	1.03	0.96 to 1.11	< .001§
Buccal cavity, pharynx	24	0.90	0.57 to 1.33	21	1.20	0.74 to 1.83	10	0.67	0.32 to 1.23	0.3
Salivary gland	9	2.81§	1.28 to 5.33	4	1.95	0.53 to 4.98	< 3	0.59	0.01 to 3.28	
Esophagus	17	1.16	0.67 to 1.85	6	0.67	0.25 to 1.47	3	0.41	0.08 to 1.20	
Stomach	23	0.89	0.56 to 1.33	13	0.76	0.41 to 1.30	15	1.15	0.64 to 1.89	.5
Colon excluding rectum	139	1.20§	1.01 to 1.42	85	1.19	0.95 to 1.47	65	1.11	0.86 to 1.42	> .5
Rectum, rectosigmoid junction	43	1.11	0.80 to 1.49	19	0.76	0.46 to 1.18	15	0.72	0.40 to 1.19	.3
Anus, anal canal, anorectum	8	2.44§	1.05 to 4.80	4	1.74	0.47 to 4.45	< 3	0.49	0.01 to 2.73	
Liver	12	0.86	0.44 to 1.49	16	1.55	0.89 to 2.52	9	1.13	0.52 to 2.15	
Pancreas	37	1.02	0.72 to 1.41	32	1.39	0.95 to 1.97	9§	0.48§	0.22 to 0.91§	
Larynx	9	0.83	0.38 to 1.58	9	1.39	0.63 to 2.63	6	1.09	0.40 to 2.37	
Lung, bronchus	274	1.42§	1.26 to 1.60	120	1.00	0.83 to 1.19	129	1.28§	1.07 to 1.53	.001§
Bones and joints	0			3	3.89	0.80 to 11.38	3	4.73	0.97 to 13.81	
Soft tissue including heart	7	1.13	0.45 to 2.33	7	1.66	0.67 to 3.42	3	0.87	0.18 to 2.54	
Melanoma of the skin	85	1.92§	1.53 to 2.37	31	1.06	0.72 to 1.50	41	1.60§	1.15 to 2.17	.004§
Female breast	122	1.01	0.84 to 1.20	102	1.06	0.87 to 1.29	68	0.74§	0.58 to 0.94	.06
Male breast	5	2.63	0.85 to 6.13	0			0			
Cervix uteri	< 3	0.50	0.06 to 1.80	3	0.77	0.16 to 2.24	3	0.84	0.17 to 2.44	
Corpus uteri	18	0.76	0.45 to 1.20	23	1.24	0.79 to 1.86	17	0.95	0.55 to 1.52	.3
Ovary	19	1.36	0.82 to 2.13	9	0.84	0.38 to 1.59	9	0.90	0.41 to 1.70	
Prostate	272	0.97	0.85 to 1.09	156	0.97	0.83 to 1.14	113	0.86	0.71 to 1.03	.5
Urinary bladder	76	0.96	0.76 to 1.20	49	1.07	0.79 to 1.41	43	1.16	0.84 to 1.57	> .5
Kidney	38	1.28	0.91 to 1.76	23	1.19	0.75 to 1.78	21	1.26	0.78 to 1.93	> .5
Brain, central nervous system	11	0.89	0.44 to 1.59	8	0.95	0.41 to 1.87	6	0.83	0.30 to 1.80	
Thyroid	18	2.07§	1.23 to 3.27	12	1.48	0.77 to 2.59	5	0.69	0.22 to 1.62	
Hodgkin's lymphoma	41	15.11§	10.85 to 20.50	20	9.02§	5.51 to 13.93	12	6.78§	3.50 to 11.85	.009§
Multiple myeloma	20	1.13	0.69 to 1.75	7	0.64	0.26 to 1.33	3	0.33§	0.07 to 0.97	
Acute nonlymphocytic leukemia	13	1.13	0.60 to 1.93	36	4.96§	3.47 to 6.87	35	5.96§	4.15 to 8.29	< .001§
Chronic myeloid leukemia	4	0.90	0.24 to 2.29	7	2.50§	1.00 to 5.15	4	1.75	0.48 to 4.49	
Kaposi's sarcoma	4	3.37	0.92 to 8.62	0			0			
Other	109	1.39§	1.14 to 1.68	52	1.03	0.77 to 1.36	37	0.90	0.63 to 1.24	.02§
Patients with known HIV/AIDS†										
All second primary malignancies‡	< 3	2.65	0.32 to 9.56	49	3.81§	2.82 to 5.03	3	1.07	0.22 to 3.12	
Buccal cavity, pharynx	0			3	5.94§	1.22 to 17.36	0			
Anus, anal canal, anorectum	0			7	120.50§	48.45 to 248.28	0			
Hodgkin's lymphoma	0			5	47.56§	15.44 to 110.99	0			
Acute nonlymphocytic leukemia	0			3	27.65§	5.70 to 80.79	0			
Kaposi's sarcoma	0			16	138.90§	79.39 to 225.56	< 3§	181.86§	22.02 to 656.95	
Other	< 3	2.78	0.34 to 10.03	15	1.25	0.70 to 2.06	< 3	0.37	0.01 to 2.08	

NOTE. To enable comparison of our results with previous studies, second primary malignancy risks after all non-Hodgkin's lymphoma combined (excluding CLL) are presented in Appendix Table A2 (online only). Second primary malignancies with significantly increased risks included lung/bronchus (SIR = 1.19), bones and joints (SIR = 3.62), cutaneous melanoma (SIR = 1.44), urinary bladder (SIR = 1.17), Hodgkin's lymphoma (SIR = 7.88), acute nonlymphocytic leukemia (SIR = 4.65), and chronic myeloid leukemia (SIR = 2.67); those with significantly decreased risks included rectum/rectosigmoid junction (O = 67; SIR = 0.73) and prostate (SIR = 0.92). Exact cell counts with fewer than three patients are suppressed to protect patient confidentiality.

Abbreviations: CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; SEER, Surveillance, Epidemiology, and End Results; O, observed; SIR, standardized incidence ratio.

*Differences in the second malignancy risks among the lymphoma subtypes were tested for second cancers with at least 10 observed occurrences for all three lymphoma subtypes, using a likelihood ratio test derived from Poisson regression models stratified by age at lymphoma diagnosis, sex, and latency.

†HIV/AIDS status was coded directly from the medical record at the time of initial non-Hodgkin's lymphoma (ie, SLL, DLBCL, FL) diagnosis. SEER does not collect information on HIV/AIDS status for patients with CLL. We assumed that all patients with CLL did not have HIV/AIDS-related disease.

‡All second primary malignancies excluding non-Hodgkin's lymphoma, lymphocytic leukemia, and nonmelanoma skin cancer.

§P < .05.

||Em dashes indicate cells for which SIR and 95% CI were not reported, when there were zero observed occurrences.

sex, latency, initial treatment, and melanoma site and thickness were not significant.

Although risk for Hodgkin's lymphoma was elevated after all three lymphoma types, the magnitude of the excess differed by sub-

type, with the largest risks observed after CLL/SLL (SIR: CLL/SLL = 15.11; DLBCL = 9.02; FL = 6.78; $P_{\text{Diff}} = .009$). Most noteworthy were the greater than 20-fold risks of Hodgkin's lymphoma observed for patients diagnosed with CLL/SLL before age 70 years ($P_{\text{trend}} = .02$;

Table 3. Risk for Second Primary Lung and Bronchus Cancer by Age, Sex, Latency, Initial Treatment, and Histology Among Patients Without Known HIV/AIDS Surviving at Least 1 Year After an Initial Diagnosis of CLL/SLL, DLBCL, or FL in 11 SEER Registries, 1992-2006

Variable	Diagnosis								
	CLL/SLL			DLBCL			FL		
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Age, years									
< 55	23	2.32*	1.47 to 3.49	11	1.03	0.52 to 1.85	23	2.01*	1.27 to 3.01
55-69	121	1.52*	1.26 to 1.82	51	1.02	0.76 to 1.34	58	1.29	0.98 to 1.67
≥ 70	130	1.26*	1.05 to 1.49	58	0.98	0.74 to 1.26	48	1.09	0.80 to 1.44
<i>P</i> _{trend} †		.005*			> .5			.01*	
Sex									
Male	173	1.40*	1.20 to 1.62	69	0.98	0.76 to 1.24	60	1.08	0.83 to 1.39
Female	101	1.47*	1.20 to 1.78	51	1.03	0.76 to 1.35	69	1.53*	1.19 to 1.94
<i>P</i> _{homogeneity} †		> .5			> .5			.04*	
Latency, years									
1-4	180	1.46*	1.25 to 1.69	75	0.99	0.78 to 1.24	84	1.37*	1.09 to 1.69
5-9	77	1.34*	1.06 to 1.67	36	0.99	0.69 to 1.37	37	1.16	0.82 to 1.60
≥ 10	17	1.45	0.84 to 2.31	9	1.15	0.53 to 2.19	8	1.12	0.48 to 2.21
<i>P</i> _{trend} †		.3			> .5			.1	
First course of treatment									
Any radiation	13	2.16*	1.15 to 3.69	37	0.91	0.64 to 1.26	33	1.38	0.95 to 1.94
No/unknown radiation	261	1.40*	1.23 to 1.58	83	1.04	0.83 to 1.29	96	1.25*	1.02 to 1.53
<i>P</i> _{homogeneity} †		.2			> .5			> .5	
Chemotherapy									
Any chemotherapy	101	1.90*	1.55 to 2.31	93	0.95	0.77 to 1.17	69	1.37*	1.07 to 1.74
No/unknown chemotherapy	173	1.24*	1.06 to 1.44	27	1.20	0.79 to 1.74	60	1.19	0.91 to 1.54
<i>P</i> _{homogeneity} *†		.002*			.3			> .5	
Histology									
Small-cell carcinoma	25	1.08	0.70 to 1.60	12	0.82	0.43 to 1.44	12	0.95	0.49 to 1.65
Non-small-cell carcinoma	241	1.53*	1.34 to 1.73	104	1.06	0.86 to 1.28	115	1.40*	1.16 to 1.68
Squamous cell carcinoma	53	1.41*	1.06 to 1.85	28	1.26	0.83 to 1.81	25	1.35	0.88 to 2.00
Adenocarcinoma	103	1.68*	1.37 to 2.03	52	1.31	0.98 to 1.72	54	1.61*	1.21 to 2.10
Other non-small-cell carcinoma	85	1.45*	1.16 to 1.79	24	0.66	0.42 to 0.98	36	1.20	0.84 to 1.66
Other	8	0.67	0.29 to 1.31	4	0.56	0.15 to 1.43	<3	0.36	0.04 to 1.30

NOTE. HIV/AIDS status was coded directly from the medical record at the time of initial non-Hodgkin's lymphoma (ie, SLL, DLBCL, FL) diagnosis. SEER does not collect information on HIV/AIDS status for patients with CLL. Therefore, we assumed that all patients with CLL did not have HIV/AIDS-related disease. Exact cell counts with fewer than three patients are suppressed to protect patient confidentiality.

Abbreviations: CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; SEER, Surveillance, Epidemiology, and End Results; O, observed; SIR, standardized incidence ratio.

**P* < .05.

†*P* values to test differences in the SIRs within each lymphoma subtype were computed by using a likelihood ratio test derived from Poisson regression models stratified by age at lymphoma diagnosis, sex, and latency (except when these variables were under evaluation).

Table 5). Initial chemotherapy also appeared to heighten risk of Hodgkin's lymphoma after CLL/SLL. When we evaluated risks among CLL and SLL patients separately, Hodgkin's lymphoma risk was higher after CLL than SLL (Appendix Table A1). Hodgkin's lymphoma risk after DLBCL and FL did not differ significantly by age, sex, latency, or initial treatment.

Elevated risks were observed for acute nonlymphocytic leukemia after DLBCL (SIR = 4.96) and FL (SIR = 5.96) but not after CLL/SLL (SIR = 1.13; *P*_{Diff} < .001). Initial chemotherapy contributed strongly to the increased risk of acute nonlymphocytic leukemia: 87% (ie, 62 of 71 patients) of the occurrences after DLBCL and FL developed in patients who received initial chemotherapy (Table 6). Acute nonlymphocytic leukemia risk also varied by age at DLBCL or FL diagnosis, with greater than 15-fold risks observed for patients diagnosed at younger ages (< 55 years) and a downward trend in risk with increasing age (*P*_{trend} DLBCL < .001; FL < .001). Women had greater risk of acute nonlymphocytic leukemia than men after DLBCL but not after

FL. When we evaluated the risks among patients with CLL and SLL separately, acute nonlymphocytic leukemia was elevated after SLL but not after CLL (Appendix Table 1).

Second Malignancy Risks Among DLBCL Patients With HIV/AIDS

Second malignancies occurred in 49 patients with HIV/AIDS-related DLBCL (SIR = 3.81; 95% CI, 2.82 to 5.03). As expected, risks of anal cancer (O = 7; SIR = 120.50) and Kaposi's sarcoma (O = 16; SIR = 138.90) were especially striking. On the basis of smaller numbers, elevated risks were also observed for buccal cavity cancers, Hodgkin's lymphoma, and acute nonlymphocytic leukemia.

DISCUSSION

Although previous small studies have evaluated second malignancy risks after treatment for aggressive or indolent lymphomas,^{10,16-17,19}

Table 4. Risk for Second Primary Melanoma by Age, Sex, Latency, Initial Treatment, Site, and Thickness Among Patients Without Known HIV/AIDS Surviving at Least 1 Year After an Initial Diagnosis of CLL/SLL, DLBCL, or FL in 11 SEER Registries, 1992-2006

Variable	Diagnosis								
	CLL/SLL			DLBCL			FL		
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Age, years									
< 55	14	2.89*	1.58 to 4.85	10	1.55	0.74 to 2.85	12	1.82	0.94 to 3.18
55-69	39	2.19*	1.55 to 2.99	13	1.19	0.63 to 2.03	15	1.47	0.82 to 2.43
≥ 70	32	1.48*	1.01 to 2.09	8	0.67	0.29 to 1.32	14	1.59	0.87 to 2.67
$P_{\text{trend}}^{\dagger}$		.02*			.1			> .5	
Sex									
Male	64	1.94*	1.50 to 2.48	19	0.95	0.57 to 1.49	27	1.64*	1.08 to 2.38
Female	21	1.84*	1.14 to 2.81	12	1.28	0.66 to 2.23	14	1.54	0.84 to 2.59
$P_{\text{homogeneity}}^{\dagger}$		> .5			.5			> .5	
Latency, years									
1-4	57	2.07*	1.57 to 2.68	17	0.94	0.55 to 1.51	26	1.71*	1.12 to 2.51
5-9	24	1.75*	1.12 to 2.60	10	1.09	0.52 to 2.00	11	1.31	0.66 to 2.35
≥ 10	4	1.33	0.36 to 3.40	4	1.87	0.51 to 4.78	4	1.97	0.54 to 5.06
$P_{\text{trend}}^{\dagger}$		.2			.4			> .5	
First course of treatment									
Any radiation	< 3	1.46	0.18 to 5.28	12	1.19	0.61 to 2.08	9	1.46	0.67 to 2.77
No/unknown radiation	83	1.93*	1.54 to 2.39	19	0.99	0.59 to 1.54	32	1.65*	1.13 to 2.33
$P_{\text{homogeneity}}^{\dagger}$		> .5			> .5			> .5	
Any chemotherapy	26	2.20*	1.44 to 3.23	24	1.00	0.64 to 1.48	17	1.28	0.75 to 2.05
No/unknown chemotherapy	59	1.81*	1.38 to 2.34	7	1.33	0.53 to 2.74	24	1.95*	1.25 to 2.90
$P_{\text{homogeneity}}^{\dagger}$		> .5			.5			.1	
Site									
Face/head/neck	29	2.24*	1.50 to 3.22	9	1.17	0.53 to 2.22	16	2.51*	1.44 to 4.08
Limbs	34	2.09*	1.45 to 2.92	10	0.87	0.42 to 1.61	12	1.16	0.60 to 2.03
Trunk	16	1.23	0.70 to 1.99	10	1.13	0.54 to 2.07	11	1.41	0.71 to 2.53
Other: overlapping, NOS	6*	2.87*	1.05 to 6.24	<3	1.52	0.18 to 5.49	< 3	1.78	0.22 to 6.44
$P_{\text{homogeneity}}^{\dagger\ddagger}$		.05*			> .5			.2	
Thickness, mm									
< 1.0	12	1.27	0.66 to 2.21	7	0.99	0.40 to 2.04	11	1.81	0.90 to 3.24
1.0-3.9	10	2.57*	1.23 to 4.73	4	1.46	0.40 to 3.73	6	2.64	0.97 to 5.75
≥ 4.0	9	3.30*	1.51 to 6.27	5	2.64	0.86 to 6.16	3	1.94	0.40 to 5.66
Unknown	54	1.93*	1.45 to 2.52	15	0.86	0.48 to 1.42	21	1.36	0.84 to 2.07
$P_{\text{trend}}^{\dagger\ddagger}$		.02*			.1			> .5	

NOTE. HIV/AIDS status was coded directly from the medical record at the time of initial non-Hodgkin's lymphoma (ie, SLL, DLBCL, FL) diagnosis. SEER does not collect information on HIV/AIDS status for patients with CLL. We assumed that all patients with CLL did not have HIV/AIDS-related disease. Exact cell counts with fewer than three patients are suppressed to protect patient confidentiality.

Abbreviations: CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; SEER, Surveillance, Epidemiology, and End Results; O, observed; SIR, standardized incidence ratio; NOS, not otherwise specified.

* $P < .05$.

$\dagger P$ values to test differences in the SIRs within each lymphoma subtype were computed by using a likelihood ratio test derived from Poisson regression models stratified by age at lymphoma diagnosis, sex, and latency (except when these variables were under evaluation).

$\ddagger$ The test for homogeneity by melanoma site and the test for trend by melanoma thickness included patients with known values only.

we provide the first quantitative comparison of second malignancy risks among survivors of the major lymphoma subtypes in a large, population-based study. Our findings demonstrate substantial heterogeneity in the occurrence of second malignancy by lymphoma subtype, which suggests differences in etiology. Specifically, we observed significantly different patterns of second malignancy after CLL/SLL, DLBCL, and FL among patients without HIV/AIDS-related lymphoma. Most notable were elevated risks for lung cancer and melanoma after the more indolent lymphomas, CLL/SLL and FL, but not after the more aggressive DLBCL. Only CLL/SLL survivors had greater risk of developing other nonhematologic malignancies (ie, salivary gland, colon, anus, and thyroid). In contrast, we found no evidence that DLBCL survivors had heightened risks for any non-

hematologic malignancy. We also observed elevated risks for Hodgkin's lymphoma after all three lymphoma subtypes, particularly CLL/SLL, and chemotherapy-related excesses of acute non-lymphocytic leukemia after DLBCL and FL.

Indolent NHLs are incurable, slow-growing lymphomas that cause few symptoms in early stages and feature a relapsing-remitting course.¹⁻² Treatment is often deferred until disease progression occurs, when an oral alkylating agent such as chlorambucil is the standard primary treatment.³⁶ Patients with relapsed or advanced disease receive various combinations of chemotherapy, radiotherapy, immunotherapy, radioimmunotherapy, or high-dose chemoradiotherapy with stem-cell transplantation.³⁶⁻³⁷ Patients with indolent NHL, particularly CLL, have well-characterized long-term immune

Table 5. Risk for Second Primary Hodgkin's Lymphoma by Age, Sex, Latency, and Initial Treatment Among Patients Without Known HIV/AIDS Surviving at Least 1 Year After an Initial Diagnosis of CLL/SLL, DLBCL, or FL in 11 SEER Registries, 1992-2006

Variable	Diagnosis								
	CLL/SLL			DLBCL			FL		
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Age, years									
< 55	9	21.47*	9.82 to 40.75	9	10.78*	4.93 to 20.47	5	8.14*	2.64 to 19.00
55-69	24	21.87*	14.01 to 32.55	6	8.66*	3.18 to 18.84	4	6.26*	1.71 to 16.02
≥ 70	8	6.69*	2.89 to 13.18	5	7.25*	2.36 to 16.93	3	5.81*	1.20 to 16.97
<i>P</i> _{trend} †		.02*			.5			> .5	
Sex									
Male	30	16.84*	11.36 to 24.04	14	10.37*	5.67 to 17.41	6	5.82*	2.13 to 12.66
Female	11	11.81*	5.90 to 21.13	6	6.92*	2.54 to 15.05	6	8.13*	2.98 to 17.69
<i>P</i> _{homogeneity} †		> .5			0.4			> .5	
Latency, years									
1-4	19	10.96*	6.60 to 17.11	14	10.12*	5.53 to 16.98	6	5.51*	2.02 to 11.99
5-9	18	22.19*	13.15 to 35.07	5	7.34*	2.38 to 17.12	6	10.81*	3.97 to 23.52
≥ 10	4	23.85*	6.50 to 61.06	< 3	6.57	0.17 to 36.63	0	‡	
<i>P</i> _{trend} †		.09			.4			> .5	
First course of treatment									
Any radiation	< 3	21.43*	2.60 to 77.42	9	11.45*	5.24 to 21.73	< 3	4.75	0.58 to 17.17
No/unknown radiation	39	14.89*	10.59 to 20.35	11	7.69*	3.84 to 13.75	10	7.41*	3.56 to 13.63
<i>P</i> _{homogeneity} †		> .5			.4			> .5	
Any chemotherapy	28	36.62*	24.33 to 52.92	15	8.16*	4.57 to 13.45	5	5.31*	1.73 to 12.40
No/unknown chemotherapy	13	6.67*	3.55 to 11.41	5	13.22*	4.29 to 30.84	7	8.45*	3.40 to 17.40
<i>P</i> _{homogeneity} †		< .001*			.3			.4	

NOTE. HIV/AIDS status was coded directly from the medical record at the time of initial non-Hodgkin's lymphoma (ie, SLL, DLBCL, FL) diagnosis. SEER does not collect information on HIV/AIDS status for patients with CLL. We assumed that all patients with CLL did not have HIV/AIDS-related disease. Exact cell counts with fewer than three patients are suppressed to protect patient confidentiality.

Abbreviations: CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; SEER, Surveillance, Epidemiology, and End Results; O, observed; SIR, standardized incidence ratio.

**P* < .05.

†*P* values to test differences in the SIRs within each lymphoma subtype were computed by using a likelihood ratio test derived from Poisson regression models stratified by age at lymphoma diagnosis, sex, and latency (except when these variables were under evaluation).

‡SIR and 95%CI were not reported when there were zero observed occurrences.

dysfunction because of prediagnostic immune alterations, a relapsing-remitting disease course, and repeated exposure to immunosuppressive therapies over time.³⁸⁻³⁹ In contrast, aggressive NHLs such as DLBCL are rapidly growing, and 30% to 50% of patients are cured with intensive initial chemotherapy with or without radiotherapy.¹⁻² The standard chemotherapy regimen for DLBCL includes cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), combined with rituximab (CHOP-R) in recent years.⁴⁰ Patients refractory to initial therapy receive additional chemotherapy and high-dose chemoradiotherapy with stem-cell transplantation, though prognosis is generally poor.⁴⁰

We observed excesses of lung cancer and melanoma after the more indolent lymphomas, CLL/SLL and FL, but not after the more aggressive DLBCL. Numerous studies of NHL and CLL have demonstrated associations for lung cancer^{10,13,14,17,18,22,25,27-29} and melanoma,^{11-13,15,22,29,30} but the mechanisms are unclear. Immunological alterations associated with lymphomas are likely to contribute, because lung cancer and melanoma occur in excess in immunosuppressed patients,⁴¹⁻⁴³ and inflammation and infections increase lung cancer risk.⁴⁴ However, it is noteworthy that these tumors were not associated with DLBCL, the subtype most strongly linked with immune dysfunction.⁶ Because the excesses of lung cancer and melanoma were limited to more indolent lymphomas, it is plausible that long-term immune dysfunction from underlying disease or repeated

treatments is responsible. However, the excess risks immediately after CLL/SLL and FL diagnosis suggest an intrinsic mechanism, possibly involving prediagnostic immune alterations or defects in cell cycle and apoptosis, which are more characteristic of indolent than aggressive lymphomas.⁴⁵

Among Hodgkin's lymphoma survivors, epidemiologic studies have suggested that lung cancer risk is increased by radiotherapy and chemotherapy, alone or in combination with cigarette smoking.⁴⁶⁻⁴⁷ These exposures may also contribute to excess lung cancer risk seen in some studies of NHL and CLL survivors.^{10,17,18,27,48} Although FL and CLL, but not DLBCL, may be weakly related to cigarette smoking,^{49,50} the lack of association with small-cell carcinomas of the lung or other strongly tobacco-related cancers argue against smoking as a primary explanation for our findings. Additional research is warranted to confirm that excess lung cancer risks are confined to CLL/SLL and FL survivors and to evaluate the effects of treatment and shared environmental and genetic risk factors. Studies that include longer-term survivors will be necessary to consider effectively the role of radiotherapy.

In this study and others, the association between NHL and melanoma occurred at all latency periods and was not clearly related to initial treatment, which suggests the influence of shared risk factors. The main environmental risk factor for melanoma, sun exposure, appears to be protective for NHL across the major subtypes.⁵¹ We therefore hypothesize that underlying immunologic and genetic risk

Table 6. Risk for Second Primary Acute Nonlymphocytic Leukemia by Age, Sex, Latency, and Initial Treatment Among Patients Without Known HIV/AIDS Surviving at Least 1 Year After an Initial Diagnosis of CLL/SLL, DLBCL, or FL in 11 SEER Registries, 1992-2006

Variable	Diagnosis								
	CLL/SLL			DLBCL			FL		
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Age, years									
< 55	< 3	1.66	0.04 to 9.24	13	15.85*	8.44 to 27.11	14	17.68*	9.67 to 29.67
55-69	8	2.10	0.91 to 4.14	11	4.55*	2.27 to 8.14	11	5.15*	2.57 to 9.22
≥ 70	4	0.56	0.15 to 1.44	12	2.98*	1.54 to 5.21	10	3.40*	1.63 to 6.25
<i>P</i> _{trend} †		.05*			< .001*			< .001*	
Sex									
Male	11	1.46	0.73 to 2.62	12	2.76*	1.42 to 4.81	21	6.31*	3.91 to 9.65
Female	< 3	0.50	0.06 to 1.81	24	8.26*	5.29 to 12.29	14	5.51*	3.01 to 9.24
<i>P</i> _{homogeneity} †		.2			< .001*			> .5	
Latency, years									
1-4	9	1.23	0.56 to 2.33	26	5.69*	3.72 to 8.34	19	5.32*	3.20 to 8.30
5-9	4	1.15	0.31 to 2.95	9	4.06*	1.86 to 7.71	13	6.92*	3.69 to 11.84
≥ 10	0	‡		< 3	2.12	0.05 to 11.79	3	7.18*	1.48 to 20.98
<i>P</i> _{trend} †		.3			.04*			> .5	
First course of treatment									
Any radiation	0	‡		15	6.04*	3.38 to 9.96	7	5.01*	2.01 to 10.32
No/unknown radiation	13	1.17	0.62 to 2.00	21	4.40*	2.72 to 6.72	28	6.26*	4.16 to 9.05
<i>P</i> _{homogeneity} †		‡			0.4			> 0.5	
Any chemotherapy	7	2.30*	0.92 to 4.74*	32	5.48*	3.75 to 7.74	30	10.37*	7.00 to 14.80
No/unknown chemotherapy	6	0.71	0.26 to 1.54	4	2.81	0.77 to 7.20	5	1.68	0.55 to 3.92
<i>P</i> _{homogeneity} †		.06			.3			< .001*	

NOTE. HIV/AIDS status was coded directly from the medical record at the time of initial non-Hodgkin's lymphoma (ie, SLL, DLBCL, FL) diagnosis. SEER does not collect information on HIV/AIDS status for patients with CLL. We assumed that all patients with CLL did not have HIV/AIDS-related disease. Exact cell counts with fewer than three patients are suppressed to protect patient confidentiality.

Abbreviations: CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; SEER, Surveillance, Epidemiology, and End Results; O, observed; SIR, standardized incidence ratio.

**P* < .05.

†*P* values to test differences in the SIRs within each lymphoma subtype were computed by using a likelihood ratio test derived from Poisson regression models stratified by age at lymphoma diagnosis, sex, and latency (except when these variables were under evaluation).

‡SIR and 95% CI were not reported when there were zero observed occurrences.

factors contribute to the association between melanoma, CLL/SLL, and FL.⁵² Although the association between NHL and melanoma may be influenced by heightened medical surveillance, the excess risks seen for melanomas ≥ 1 mm thick but not for early lesions reduces the likelihood of this explanation.

We observed elevated Hodgkin's lymphoma risks among all NHL survivors, which is consistent with previous studies.^{11,13,17,22} Although immune dysfunction and shared risk factors may contribute to multiple, distinct lymphoid neoplasms,^{42,53-54} diagnosis of Hodgkin's lymphoma after NHL may be complicated by overlapping morphologies that lead to diagnostic misclassification between recurrence and a second malignancy, under-reporting of a second lymphoma subtype, or histologic transformation.⁵⁵ CLL/SLL propensity for transformation (ie, Richter's syndrome)⁵⁶ may contribute to the higher risks seen after CLL than other subtypes. Additional research with serial clinical evaluation, detailed pathologic review, and evaluation of tumor clonality to identify transformation is necessary to clarify whether Hodgkin's lymphoma risks vary by NHL subtype.

The increased risk for acute nonlymphocytic leukemia after DLBCL and FL was primarily seen among patients receiving initial chemotherapy, especially in younger patients. This observation is consistent with previous studies that have implicated DNA-damaging agents, such as alkylating agents and topoisomerase II inhibitors, as well as nucleoside analogs in some studies.^{10,16-18,21,22,26} Acute non-

lymphocytic leukemia risks after DLBCL and FL have not been compared previously. Although DLBCL patients receive more aggressive initial chemotherapy, our data raise the hypothesis that FL and DLBCL survivors may eventually receive similar amounts of chemotherapy because of the high risk of FL relapse and multiple courses of chemotherapy.² The increased risk after SLL but not CLL may be due to more frequent use of chemotherapy for SLL than CLL (44% v 25%).

Second malignancy risks were strikingly different in patients with HIV/AIDS-related lymphoma compared with patients without HIV/AIDS. The substantially elevated Kaposi's sarcoma risk after HIV/AIDS-related DLBCL is most likely due to the etiologic role of HIV in both malignancies,⁵⁷ whereas the excesses of buccal cavity/pharynx and anal cancers are likely related to coinfection with HIV and human papillomavirus.⁵⁸

The primary strength of our study was analysis of a large number of lymphoma survivors identified via population-based registry data, which eliminated the selection bias seen in hospital-based series. Additional strengths include the quantitative assessment of second malignancy risks by lymphoma subtype, distinction of patients with and without HIV/AIDS-related lymphoma, and the first comparison of malignancy risks after CLL and SLL. The similar patterns of second malignancy after CLL and SLL reinforces the notion that these diseases are different clinical manifestations of the same entity.¹ We limited our analysis to patients diagnosed with lymphoma in 1992 or later

to utilize the available HIV/AIDS data and to minimize lymphoma subtype misclassification.³⁴ Although this restriction precluded comprehensive assessment of second malignancy risks among long-term lymphoma survivors, elevated risks were observed within the first 5 years after lymphoma diagnosis. Additional limitations included under-ascertainment of second malignancy risks as a result of patient migration outside SEER program areas and incomplete data on the initial course of chemotherapy, which may have attenuated our results.

In summary, our findings revealed substantial differences in second malignancy risks after CLL/SLL, DLBCL, and FL. Variations in immunologic alterations, treatments (eg, alkylating agent chemotherapy), genetic susceptibility, and other risk factors (eg, viral infections, tobacco use) among lymphoma subtypes are likely to contribute to the patterns of second malignancy risk and may provide etiologic clues to lymphoma as well.

REFERENCES

- World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France, IARC Press, 2008
- DeVita VT Jr, Lawrence TS, Rosenberg SA. Cancer: Principles & Practice of Oncology (ed 8). Philadelphia, PA, Lippincott, Williams, & Wilkins, 2008
- Surveillance, Epidemiology, and End Results (SEER) Program: SEER Stat Database: Incidence—SEER 13 Regs Limited-Use, November 2008 Submission (1992-2006). National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch, 2009
- Coté TR, Biggar RJ, Rosenberg PS, et al: Non-Hodgkin's lymphoma among people with AIDS: Incidence, presentation and public health burden—AIDS/Cancer Study Group. *Int J Cancer* 73:645-650, 1997
- de Sanjose S, Benavente Y, Vajdic CM, et al: Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium. *Clin Gastroenterol Hepatol* 6:451-458, 2008
- Morton LM, Wang SS, Cozen W, et al: Etiologic heterogeneity among non-Hodgkin lymphoma subtypes. *Blood* 112:5150-5160, 2008
- Ekström Smedby K, Vajdic CM, Falster M, et al: Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: A pooled analysis within the InterLymph Consortium. *Blood* 111:4029-4038, 2008
- Skibola CF, Bracci PM, Halperin E, et al: Genetic variants at 6p21.33 are associated with susceptibility to follicular lymphoma. *Nat Genet* 41: 873-875, 2009
- Skibola CF, Bracci PM, Nieters A, et al: Tumor necrosis factor (TNF) and lymphotoxin-alpha (LTA) polymorphisms and risk of non-Hodgkin lymphoma in the InterLymph Consortium. *Am J Epidemiol* 171:267-276, 2010
- André M, Mounier N, Leleu X, et al: Second cancers and late toxicities after treatment of aggressive non-Hodgkin lymphoma with the ACVBP regimen: A GELA cohort study on 2837 patients. *Blood* 103:1222-1228, 2004
- Brennan P, Scélo G, Hemminki K, et al: Second primary cancers among 109 000 cases of non-Hodgkin's lymphoma. *Br J Cancer* 93:159-166, 2005
- Goggins WB, Finkelstein DM, Tsao H: Evidence for an association between cutaneous melanoma and non-Hodgkin lymphoma. *Cancer* 91: 874-880, 2001
- Hemminki K, Lenner P, Sundquist J, et al: Risk of subsequent solid tumors after non-Hodgkin's lymphoma: Effect of diagnostic age and time since diagnosis. *J Clin Oncol* 26:1850-1857, 2008
- Landgren O, Pfeiffer RM, Stewart L, et al: Risk of second malignant neoplasms among lymphoma patients with a family history of cancer. *Int J Cancer* 120:1099-1102, 2006
- McKenna DB, Stockton D, Brewster DH, et al: Evidence for an association between cutaneous malignant melanoma and lymphoid malignancy: A population-based retrospective cohort study in Scotland. *Br J Cancer* 88:74-78, 2003
- McLaughlin P, Estey E, Glassman A, et al: Myelodysplasia and acute myeloid leukemia following therapy for indolent lymphoma with fludarabine, mitoxantrone, and dexamethasone (FND) plus rituximab and interferon alpha. *Blood* 105:4573-4575, 2005
- Moser EC, Noordijk EM, van Leeuwen FE, et al: Risk of second cancer after treatment of aggressive non-Hodgkin's lymphoma: An EORTC cohort study. *Haematologica* 91:1481-1488, 2006
- Mudie NY, Swerdlow AJ, Higgins CD, et al: Risk of second malignancy after non-Hodgkin's lymphoma: A British cohort study. *J Clin Oncol* 24:1568-1574, 2006
- Sacchi S, Marcheselli L, Bari A, et al: Secondary malignancies after treatment for indolent non-Hodgkin's lymphoma: A 16-year follow-up study. *Haematologica* 93:398-404, 2008
- Travis LB, Curtis RE, Glimelius B, et al: Bladder and kidney cancer following cyclophosphamide therapy for non-Hodgkin's lymphoma. *J Natl Cancer Inst* 87:524-530, 1995
- Travis LB, Weeks J, Curtis RE, et al: Leukemia following low-dose total body irradiation and chemotherapy for non-Hodgkin's lymphoma. *J Clin Oncol* 14:565-571, 1996
- Tward JD, Wendland MM, Shrieve DC, et al: The risk of secondary malignancies over 30 years after the treatment of non-Hodgkin lymphoma. *Cancer* 107:108-115, 2006
- Callea V, Brugiatelli M, Stelitano C, et al: Incidence of second neoplasia in patients with B-cell chronic lymphocytic leukemia treated with chlorambucil maintenance chemotherapy. *Leuk Lymphoma* 47:2314-2320, 2006
- Cheson BD, Vena DA, Barrett J, et al: Second malignancies as a consequence of nucleoside analog therapy for chronic lymphoid leukemias. *J Clin Oncol* 17:2454-2460, 1999
- Mellemgaard A, Geisler CH, Storm HH: Risk of kidney cancer and other second solid malignancies in patients with chronic lymphocytic leukemia. *Eur J Haematol* 53:218-222, 1994
- Morrison VA, Rai KR, Peterson BL, et al: Therapy-related myeloid leukemias are observed in patients with chronic lymphocytic leukemia after treatment with fludarabine and chlorambucil: Results of an InterGroup Study, Cancer and Leukemia Group B 9011. *J Clin Oncol* 20:3878-3884, 2002
- Robak T, Blonski JZ, Gora-Tybor J, et al: Second malignancies and Richter's syndrome in patients with chronic lymphocytic leukaemia treated with cladribine. *Eur J Cancer* 40:383-389, 2004
- Schöllkopf C, Rosendahl D, Rostgaard K, et al: Risk of second cancer after chronic lymphocytic leukemia. *Int J Cancer* 121:151-156, 2007
- Travis LB, Curtis RE, Hankey BF, et al: Second cancers in patients with chronic lymphocytic leukemia. *J Natl Cancer Inst* 84:1422-1427, 1992
- Tsimberidou AM, Wen S, McLaughlin P, et al: Other malignancies in chronic lymphocytic leukemia/small lymphocytic lymphoma. *J Clin Oncol* 27: 904-910, 2009
- Clarke CA, Glaser SL: Population-based surveillance of HIV-associated cancers: Utility of cancer registry data. *J Acquir Immune Defic Syndr* 36:1083-1091, 2004
- Diamond C, Taylor TH, Im T, et al: How valid is using cancer registries data to identify acquired immunodeficiency syndrome-related non-Hodgkin's lymphoma? *Cancer Causes Control* 18:135-142, 2007
- Fritz AG: International classification of diseases for oncology (ed 3). Geneva, Switzerland, World Health Organization, 2000
- Morton LM, Turner JJ, Cerhan JR, et al: Proposed classification of lymphoid neoplasms for epidemiologic research from the Pathology Working Group of the International Lymphoma Epidemiology Consortium (InterLymph). *Blood* 110:695-708, 2007
- US Census Bureau, Population Division, Census 2000: Migration by sex and age for the population 5 years and over for the United States, regions, states, and Puerto Rico: 2000 (PHC-T-23). <http://www.census.gov/population/www/cen2000/briefs/phc-t23/index.html>

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Lindsay M. Morton, Rochelle E. Curtis, Martha S. Linet, Elizabeth C. Bluhm

Collection and assembly of data: Lynn A.G. Ries

Data analysis and interpretation: Lindsay M. Morton, Rochelle E. Curtis, Martha S. Linet, Elizabeth C. Bluhm, Margaret A. Tucker, Neil Caporaso, Lynn A.G. Ries, Joseph F. Fraumeni Jr

Manuscript writing: All authors

Final approval of manuscript: All authors

36. Gribben JG: How I treat indolent lymphoma. *Blood* 109:4617-4626, 2007
37. Vidal L, Gafter-Gvili A, Leibovici L, et al: Rituximab maintenance for the treatment of patients with follicular lymphoma: Systematic review and meta-analysis of randomized trials. *J Natl Cancer Inst* 101:248-255, 2009
38. Dasanu CA: Intrinsic and treatment-related immune alterations in chronic lymphocytic leukemia and their impact for clinical practice. *Expert Opin Pharmacother* 9:1481-1494, 2008
39. Landgren O, Albitar M, Ma W, et al: B-cell clones as early markers for chronic lymphocytic leukemia. *N Engl J Med* 360:659-667, 2009
40. Friedberg JW, Fisher RI: Diffuse large B-cell lymphoma. *Hematol Oncol Clin North Am* 22:941-952, ix, 2008
41. Chaturvedi AK, Pfeiffer RM, Chang L, et al: Elevated risk of lung cancer among people with AIDS. *AIDS* 21:207-213, 2007
42. Grulich AE, van Leeuwen MT, Falster MO, et al: Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: A meta-analysis. *Lancet* 370:59-67, 2007
43. Rizzo JD, Curtis RE, Socié G, et al: Solid cancers after allogeneic hematopoietic cell transplantation. *Blood* 113:1175-1183, 2009
44. Engels EA: Inflammation in the development of lung cancer: Epidemiological evidence. *Expert Rev Anticancer Ther* 8:605-615, 2008
45. Reed JC, Kitada S, Kim Y, et al: Modulating apoptosis pathways in low-grade B-cell malignancies using biological response modifiers. *Semin Oncol* 29:10-24, 2002 (suppl 2)
46. Swerdlow AJ, Schoemaker MJ, Allerton R, et al: Lung cancer after Hodgkin's disease: A nested case-control study of the relation to treatment. *J Clin Oncol* 19:1610-1618, 2001
47. Travis LB, Gospodarowicz M, Curtis RE, et al: Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. *J Natl Cancer Inst* 94:182-192, 2002
48. Musolino A, Bozzetti C, Bonomini S, et al: Lung cancer in patients with chronic lymphocytic leukemia: Does the HER-2 oncogene play a role? *Lung Cancer* 50:419-420, 2005
49. Morton LM, Hartge P, Holford TR, et al: Cigarette smoking and risk of non-Hodgkin lymphoma: A pooled analysis from the International Lymphoma Epidemiology Consortium. *Cancer Epidemiol Biomarkers Prev* 14:925-933, 2005
50. Richardson DB, Terschüren C, Pohlabein H, et al: Temporal patterns of association between cigarette smoking and leukemia risk. *Cancer Causes Control* 19:43-50, 2008
51. Kricker A, Armstrong BK, Hughes AM, et al: Personal sun exposure and risk of non-Hodgkin lymphoma: A pooled analysis from the InterLymph Consortium. *Int J Cancer* 122:144-154, 2008
52. Curtin JA, Fridlyand J, Kageshita T, et al: Distinct sets of genetic alterations in melanoma. *N Engl J Med* 353:2135-2147, 2005
53. Goldin LR, Landgren O, McMaster ML, et al: Familial aggregation and heterogeneity of non-Hodgkin lymphoma in population-based samples. *Cancer Epidemiol Biomarkers Prev* 14:2402-2406, 2005
54. Goldin LR, Pfeiffer RM, Gridley G, et al: Familial aggregation of Hodgkin lymphoma and related tumors. *Cancer* 100:1902-1908, 2004
55. Amini RM, Enblad G: Relationship between Hodgkin's and non-Hodgkin's lymphomas. *Med Oncol* 20:211-220, 2003
56. Tsimberidou AM, Keating MJ: Richter syndrome: Biology, incidence, and therapeutic strategies. *Cancer* 103:216-228, 2005
57. Engels EA, Biggar RJ, Hall HI, et al: Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer* 123:187-194, 2008
58. Chaturvedi AK, Madeleine MM, Biggar RJ, et al: Risk of human papillomavirus-associated cancers among persons with AIDS. *J Natl Cancer Inst* 101:1120-1130, 2009