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ORIGINAL REPORT

Risk Factors for Melanoma Among Survivors of Non-Hodgkin Lymphoma

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ABSTRACT

Purpose
Previous studies have reported that survivors of non-Hodgkin lymphoma (NHL) have an increased risk of developing cutaneous melanoma; however, risks associated with specific treatments and immune-related risk factors have not been quantified.

Patients and Methods
We evaluated second melanoma risk among 44,870 1-year survivors of first primary NHL diagnosed at age 66 to 83 years from 1992 to 2009 and included in the Surveillance, Epidemiology, and End Results-Medicare database. Information on NHL treatments, autoimmune diseases, and infections was derived from Medicare claims.

Results
A total of 202 second melanoma cases occurred among survivors of NHL, including 91 after chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and 111 after other NHL subtypes (cumulative incidence by age 85 years: CLL/SLL, 1.37%; other NHL subtypes, 0.78%). Melanoma risk after CLL/SLL was significantly increased among patients who received infused fludarabine-containing chemotherapy with or without rituximab (n = 18: hazard ratio [HR], 1.92; 95% CI, 1.09 to 3.40; n = 10: HR, 2.92; 95% CI, 1.42 to 6.01, respectively). Significantly elevated risks also were associated with T-cell activating autoimmune diseases diagnosed before CLL/SLL (n = 36: HR, 2.27; 95% CI, 1.34 to 3.84) or after CLL/SLL (n = 49: HR, 2.92; 95% CI, 1.66 to 5.12). In contrast, among patients with other NHL subtypes, melanoma risk was not associated with specific treatments or with T-cell/B-cell immune conditions. Generally, infections were not associated with melanoma risk, except for urinary tract infections (CLL/SLL), localized scleroderma, pneumonia, and gastrohepatic infections (other NHLs).

Conclusion
Our findings suggest immune perturbation may contribute to the development of melanoma after CLL/SLL. Increased vigilance is warranted among survivors of NHL to maximize opportunities for early detection of melanoma.

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INTRODUCTION

Treatment advances have substantially improved prognosis after diagnosis of non-Hodgkin lymphoma (NHL), with 5-year relative survival increasing from 47% to 71% during the past four decades.[1] However, second malignancy is an important cause of morbidity and mortality among the more than 700,000 survivors of NHL in the United States today.[2] Compared with the general population, survivors of NHL have an increased risk of developing melanoma, with particularly elevated risks among survivors of more indolent NHLs, specifically chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; standardized incidence ratio, 1.92) and, to a lesser extent, follicular lymphoma (FL; standardized incidence ratio, 1.60).[3]

Factors that may explain the increased risk of developing melanoma after NHL remain unknown. In addition to immune deficits, chemotherapy for NHL has been implicated, but previous studies have lacked detailed treatment data or sufficient numbers of second melanoma cases to investigate associations with specific chemotherapeutic agents.[3-21] Increased melanoma risk in immunosuppressed patients[22-27] supports a potential role for immune dysfunction in the development of melanoma after NHL, either independently or in conjunction

with UV radiation via sun exposure, a major risk factor for melanoma.[5,15-21] However, no previous study has had data on these factors to investigate the hypothesized associations. We therefore used the Surveillance, Epidemiology, and End Results-Medicare (SEER-Medicare) linkage to quantify the risk of developing second cutaneous melanoma in relation to NHL treatments and immune-related medical conditions among 44,870 survivors of first primary NHL in the US older adult population.

PATIENTS AND METHODS

Study Population

Eligible patients were identified through the SEER-Medicare linkage,[28] including men and women diagnosed with first primary NHL between age 66 and 83 years from 1992 to 2009. First primary NHL cases were identified in SEER (Table 1).[29-31] Patients must have had continuous fee-for-service Medicare parts A and B coverage for 12 months or longer before and after NHL diagnosis for ascertainment of treatment and medical conditions. NHL diagnoses and follow-up time at age 85 years and older were excluded because of under-ascertainment of second malignancies at older ages.[32] Patients who died less than 1 year after NHL diagnosis (N = 602), developed a second cancer less than 1 year after NHL diagnosis (n = 947), had HIV (n = 291), or underwent solid organ transplantation before NHL diagnosis (n = 124) were excluded. We required 1 year or longer of follow-up after NHL to allow sufficient time for completion of initial treatment before being at risk for a second melanoma, and to minimize inclusion of incidental cancer diagnoses identified during heightened medical surveillance immediately after NHL diagnosis. Second primary invasive cutaneous melanomas that developed 1 year or longer after first primary NHL were identified through SEER and classified according to site and thickness (Table 1).[33]

Table 1. Selected Characteristics of 44,870 1-Year Survivors of First Primary NHL, Overall and by NHL Subtype, Diagnosed at Age 66 to 83 Years, 16 SEER Registries, 1992 to 2009

			First Primary NHL Subtype*									
	Total NHL		CLL/SLL		DLBCL		FL		MZL		Other	
Variable	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. of 1-year survivors	44,870		13,950		10,311		7,437		3,516		9,656	
Age at NHL diagnosis, years												
66-69	9,673	21.6	2,901	20.8	2,169	21.0	1,828	24.6	767	21.8	2,008	20.8
70-74	13,120	29.2	3,982	28.5	3,038	29.5	2,243	30.2	988	28.1	2,869	29.7
75-79	12,754	28.4	4,030	28.9	2,934	28.5	1,985	26.7	958	27.3	2,847	29.5
80-83	9,323	20.8	3,037	21.8	2,170	21.1	1,381	18.6	803	22.8	1,932	20.0
Sex												
Male	22,097	49.3	7,590	54.4	4,725	45.8	3,229	43.4	1,439	40.9	5,114	53.0
Female	22,773	50.8	6,360	45.6	5,586	54.2	4,208	56.6	2,077	59.1	4,542	47.0
Race												
White	40,752	90.8	12,841	92.1	9,222	89.4	6,888	92.6	3,090	87.9	8,711	90.2
Other/unknown	4,118	9.2	1,109	7.9	1,089	10.6	549	7.4	426	12.1	945	9.8
Year of NHL diagnosis												
1992-1997†	8,127	18.1	2,755	19.8	1,798	17.4	1,345	18.1	233	6.6	1,996	20.7
1998-2003	15,978	35.6	5,002	35.9	3,680	35.7	2,618	35.2	1,317	37.5	3,361	34.8
2004-2009	20,765	46.3	6,193	44.4	4,833	46.9	3,474	46.7	1,966	55.9	4,299	44.5
Residence at time of NHL diagnosis‡												
North	20,348	45.4	6,691	48.0	4,473	43.4	3,206	43.1	1,511	43.0	4,467	46.3
Central	12,778	28.5	3,727	26.7	3,107	30.1	2,260	30.4	1,041	29.6	2,643	27.4
South	11,744	26.2	3,532	25.3	2,731	26.5	1,971	26.5	964	27.4	2,546	26.4
Median age at NHL, years	74.0		75.0		74.0		74.0		75.0		74.0	
Mean person-years at risk	5.5		5.6		5.4		5.8		5.6		5.3	
No. of second melanomas	202		91		34		34		10		33	
Median interval from NHL to melanoma, years	3.0		3.3		2.9		2.8		3.0		2.6	
Site of melanoma§												
Face/head/neck	73	36.1	37	40.7	< 10	—	11	32.3	< 10	—	14	42.4
Trunk	56	27.7	23	25.3	13	38.2	< 10	—	< 10	—	< 10	—
Upper/lower extremities, other/unspecified	73	36.1	31	34.1	13	38.2	14	41.2	< 10	—	11	33.3
Thickness of melanoma, mm										—		
< 1.0	104	51.4	41	45.1	25	73.5	16	47.1	< 10	—	16	48.5
> 1.0	70	34.7	39	42.9	< 10	—	13	38.2	< 10	—	< 10	—
Unknown	28	13.9	11	12.1	< 10	—	< 10	—	< 10	—	< 10	—

NOTE. Counts and percentages are not reported for fewer than 10 melanoma cases to protect patient confidentiality.

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; ICD-O-3 International Classification of Diseases for Oncology, 3rd Edition; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma.

*First primary NHL subtype defined by ICD-O-3 as DLBCL (9678-9680, 9684 [B cell]), FL (9690-9691, 9695, 9698), CLL/SLL (9670, 9823), MZL (9689, 9699) and other NHL (9590-9596, 9671, 9673, 9675, 9684 [non B cell], 9687, 9700-9702, 9705, 9708-9709, 9714-9719, 9727-9729, 9827 [primary site, C42.0-42.1, C42.4]).

†1992-1997 includes 13 SEER registries, whereas 1998-2003 and 2004-2009 include 16 SEER registries.

‡Residence defined by SEER registry areas, including north (Connecticut, Detroit, Iowa, Seattle, and New Jersey), central (San Francisco, Utah, San Jose, Greater California, and Kentucky), and south (Hawaii, New Mexico, Atlanta, Los Angeles, Rural Georgia, Greater Georgia, and Louisiana).

§Melanoma site defined by ICD-O-3 as face/head/neck (C44.0-C44.4), trunk (C44.5), upper extremities (C44.6), lower extremities (C44.7), and other/unspecified (C44.8-C44.9).

NHL Treatments and Medical Conditions

Information on NHL treatments (infused chemotherapy, radiotherapy, and hematopoietic stem-cell transplant) and immune-related medical conditions (nonhematologic autoimmune diseases and selected infections) was derived from Medicare claims (Appendix Tables 1, 2, and 3, online only). Data on oral chemotherapeutic agents were not available from Medicare throughout the study period and, thus, were excluded. Patients who did not receive therapy (eg, observed) or who received oral chemotherapy agents exclusively were included in our referent group.

Occurrences of autoimmune diseases and infections were defined as having one or more Medicare claims at any time during follow-up, considering diagnoses occurring before NHL separately from those occurring after NHL. Diagnoses of these conditions occurring before 1992 (study start) or Medicare enrollment (age 65 years) were not captured. We evaluated all specific autoimmune conditions and infections with 10 or more second melanoma cases. Because many diagnoses were rare, we grouped them by the tissue and organ systems involved, and (for autoimmune conditions) by whether they activate B or T cells (Table 2).[34-38] Hematologic autoimmune conditions (eg, autoimmune hemolytic anemia and thrombocytopenia) were not considered because of difficulty distinguishing these diagnoses from manifestations of chemotherapy toxicity.

Because sun exposure is a key melanoma risk factor, we grouped survivors of NHL according to their residence at the time of NHL on the basis of the SEER registry (Table 1). These categorizations, on the basis of UV-B radiation flux, have been shown to be a valid proxy for recent sun exposure in a melanoma risk model.[39]

Statistical Analysis

Follow-up began 1 year after NHL and continued until the earliest of the following: second cancer diagnosis, age 85 years, death, loss to follow-up, or end of study (December 31, 2009). We used Cox proportional hazards regression to compute hazard ratios (HRs) and 95% CIs to assess the association between specific risk factors and development of second melanoma after first primary NHL. All analyses used age as the time scale, were adjusted for demographic factors (sex, race [white or other], residence [North, Central, or South], socioeconomic status [derived using census tract–level information on household income and educational attainment], number of comorbidities[40] [0, 1, or 2+], and follow-up time as a time-dependent covariate [1 to 1.9, 2 to 2.9, 3 to 3.9, 4 to 4.9, 5 to 6.9, and $\geq$ 7 years]), and were stratified by calendar year of NHL diagnosis. Stratification by year and use of age as the time scale adjusted for differences in the gap between entrance into Medicare and NHL diagnosis. Time-dependent covariates were used to indicate receipt of radiotherapy or infused chemotherapy during follow-up on the basis of the timing of therapy initiation. For autoimmune conditions/infections occurring before NHL, we defined the follow-up period from age at enrollment into Medicare to age of NHL diagnosis. Autoimmune conditions and infections diagnosed after NHL were evaluated as time-dependent covariates on the basis of the timing of diagnoses of these conditions. Because CLL/SLL treatment patterns differ from other NHLs,[41] and because CLL/SLL survivors have a higher risk for developing melanoma,[3] we calculated risks separately for CLL/SLL and other NHL subtypes combined.

Second melanoma risk associated with NHL treatments was evaluated in multivariable models, including both chemotherapy and radiotherapy. We modeled infused chemotherapy-related risks a priori using two different approaches. First (model A), we examined risks for patients who received any of the three main chemotherapy agents (cyclophosphamide, rituximab, and fludarabine) with separate indicator variables for each agent. Second (model B), we assessed risk according to the most frequently received combinations of these agents (Table 3). For both analytic approaches, we used patients with no Medicare chemotherapy claims (ie, no infused chemotherapy) as our referent group and excluded other treatments (eg, other alkylating agents and epipodophyllotoxins) because few patients ($n < 10$) received them. In secondary analyses, we considered other agents (Appendix Table 1). A two-sided Wald χ^2 $P < .05$ comparing models with and without the factor of interest identified melanoma risk factors. For all melanoma risk factors we identified in our primary analyses, exploratory analyses investigated differences in risks by residence because of the hypothesized interaction between immune dysfunction and UV radiation.[5,15-21] To evaluate if increased melanoma risk was influenced by increased medical surveillance, we also investigated differences by melanoma thickness.[42] Finally, we calculated cumulative incidence of melanoma by age at diagnosis, taking into account death, loss to follow-up, and diagnosis of other second cancers as competing risks.[43] All analyses were conducted using SAS 9.3 (Cary, NC).

RESULTS

Our study population of 44,870 1-year survivors of first primary NHL included 13,950 individuals with CLL/SLL, 10,311 with diffuse large B-cell lymphoma (DLBCL), 7,437 with FL, 3,516 with marginal zone lymphoma, and 9,656 with other lymphoma subtypes (Table 1). The median age at diagnosis was 74 years, and most survivors (91%) were white. Greater than half of all survivors of CLL/SLL were male (54%), whereas 54% of survivors of DLBCL and 57% of survivors of FL were female. At the time of NHL diagnosis, 45% of survivors resided in northern regions, 29% in central regions, and 26% in southern regions.

During 247,883 total person-years of follow-up (mean follow-up time, 5.5 years), 202 second melanomas were diagnosed. The median interval from NHL to melanoma diagnosis was 3 years (range, 1 to 14.8 years). Melanoma risks were higher among males, non-Hispanic whites, patients residing in southern regions, and for survivors of CLL/SLL than for survivors of other NHL subtypes (Appendix Table 4, online only). Nearly half ($n = 91$, 45%) of melanomas were diagnosed after CLL/SLL, with 40.7% of these occurring on the face, head, or neck and 42.9% with 1-mm thickness or greater (Table 1). In contrast, among survivors of all other NHL subtypes combined, melanomas with specified site and depth occurred most frequently on the trunk (29.7%), and 27.9% were 1-mm thick or greater.

A total of 5,051 (36.3%) survivors of CLL/SLL received infused chemotherapy during follow-up, of whom 2,712 (53.7%) initiated chemotherapy within 12 months of diagnosis. Rituximab (26.8%), fludarabine (21.2%), and cyclophosphamide (17.2%; Table 3 and Appendix Table 1) were the most common received infused agents. Initial analyses showed second melanoma risk was significantly increased among 2,958 patients who were treated for CLL/SLL with any fludarabine-containing chemotherapy (HR, 1.90; 95% CI, 1.08 to 3.37) compared with patients not recorded as receiving infused chemotherapy or who received oral agents alone (Table 3, model A). Further analyses showed significant increased risk of developing melanoma among patients with CLL/SLL who received fludarabine-containing infused chemotherapy with rituximab (HR, 1.92; 95% CI, 1.09 to 3.40) or without rituximab (HR, 2.92; 95% CI, 1.42 to 6.01; Table 3, model B). In models adjusting for chemotherapy, treatment of CLL/SLL with radiotherapy was not associated with melanoma risk.

Among survivors of non-CLL/SLL, a total of 20,880 (67.5%) patients received infused chemotherapy during follow-up. Of those patients, 18,694 (89.5%) began chemotherapy within the first 12 months of NHL diagnosis. Rituximab (50.9%) and cyclophosphamide (54.3%) were the most common received infused agents, whereas fewer patients received fludarabine (8.1%) or other agents (7.6%; Table 3 and Appendix Table 1). Melanoma risks were not significantly increased after treatment with any

Table 2. Risk of Melanoma After First Primary NHL, by Subtype, in Relation to Autoimmune Conditions and Infections

Medical Conditions	Before NHL Diagnosis						After NHL Diagnosis*					
	Total NHL		Melanoma Cases				Total NHL		Melanoma Cases			
	No.	%	No.	%	HR†	95% CI	No.	%	No.	%	HR†	95% CI
Patients diagnosed with first primary CLL/SLL												
B-cell–activating conditions	2,263	16.2	< 10	—	0.68	0.31 to 1.49	3,637	26.1	13	14.3	0.90	0.45 to 1.83
T-cell–activating conditions	5,488	139.3	36	39.6	2.27	1.34 to 3.84	6,749	48.4	49	53.9	2.92	1.66 to 5.12
Autoimmune conditions, by organ system‡												
Systemic/connective tissue	1,687	12.1	< 10	—	0.85	0.37 to 1.98	1,912	13.7	< 10	—	1.39	0.66 to 2.93
Cardiovascular	1,367	9.8	< 10	—	1.62	0.76 to 3.45	2,370	17.0	15	16.5	2.04	1.08 to 3.85
Chronic rheumatic heart disease	1,219	8.7	< 10	—	1.88	0.88 to 4.00	2,187	15.7	15	16.5	2.31	1.23 to 4.36
Endocrine	931	6.7	< 10	—	2.56	1.21 to 5.42	1,213	8.7	< 10	—	1.43	0.57 to 3.61
Graves' disease	783	5.6	< 10	—	2.66	1.20 to 5.91	872	6.3	< 10	—	1.88	0.74 to 4.75
Skin	2,222	15.9	18	19.8	1.64	0.95 to 2.83	2,402	17.2	21	23.1	1.87	1.02 to 3.43
Localized scleroderma	1,809	13.0	12	13.2	1.21	0.65 to 2.27	1,924	13.8	13	14.3	1.43	0.72 to 2.84
Psoraisis	445	3.2	< 10	—	2.68	1.21 to 5.91	431	3.1	< 10	—	2.78	0.99 to 7.71
GI	1,435	10.3	< 10	—	0.72	0.29 to 1.81	2,926	21.0	< 10	—	0.81	0.37 to 1.78
Nervous system	110	0.8	< 10	—	0	0.0	180	1.3	< 10	—	2.33	0.32 to 17.09
Asthma	1,919	13.8	13	14.3	2.14	1.13 to 4.02	2,484	17.8	18	19.8	3.24	1.75 to 6.00
Infections, by organ system												
Respiratory, upper airway	5,847	41.9	35	38.5	1.11	0.70 to 1.77	5,850	41.9	35	38.5	0.87	0.46 to 1.63
Pharyngitis	2,141	15.4	10	11.0	0.87	0.45 to 1.71	2,143	15.4	11	12.1	1.01	0.48 to 2.12
Sinusitis	4,074	29.2	24	26.4	1.28	0.78 to 2.11	4,238	30.4	29	31.9	1.36	0.75 to 2.45
Respiratory, lower airway	6,122	43.9	37	40.7	1.27	0.79 to 2.07	8,347	59.8	41	45.1	0.89	0.49 to 1.63
Acute bronchitis	4,526	32.4	27	29.7	1.38	0.84 to 2.25	5,081	36.4	34	37.4	1.47	0.81 to 2.64
Pneumonia	2,872	20.6	16	17.6	1.19	0.67 to 2.11	6,414	46.0	21	23.1	0.85	0.47 to 1.53
Skin	2,125	15.2	17	18.7	1.67	0.96 to 2.90	3,490	25.0	21	23.1	1.47	0.84 to 2.59
Cellulitis	1,191	8.5	11	12.1	1.95	1.02 to 3.74	1,948	14.0	11	12.1	1.37	0.67 to 2.78
Urinary tract	6,227	44.6	39	42.9	1.65	0.99 to 2.76	7,942	56.9	46	50.6	2.12	1.19 to 3.77
Cystitis/pyelonephritis, UTI	5,630	40.4	34	37.4	1.81	1.08 to 3.01	7,599	54.5	40	44.0	2.17	1.24 to 3.78
Prostatitis§	1,554	20.5	17	23.0	1.29	0.73 to 2.28	1,199	15.8	14	18.9	1.73	0.80 to 3.78
Gastrohepatic	2,084	14.9	11	12.1	1.06	0.55 to 2.02	2,594	18.6	12	13.2	1.27	0.64 to 2.52
Gastroenteritis	2,020	14.5	11	12.1	1.07	0.56 to 2.05	2,445	17.5	11	12.1	1.19	0.58 to 2.43
Patients diagnosed with first primary NHL other than CLL/SLL												
B-cell–activating conditions	6,013	19.5	16	14.4	1.14	0.65 to 1.98	8,078	26.1	24	21.6	1.56	0.88 to 2.76
T-cell–activating conditions	13,142	42.5	36	32.4	0.93	0.59 to 1.45	15,201	49.2	35	31.5	1.13	0.67 to 1.88
Autoimmune conditions, by organ system												
Systemic/connective tissue	4,798	15.5	< 10	—	0.59	0.28 to 1.23	4,734	15.3	< 10	—	0.69	0.28 to 1.73
Cardiovascular	3,212	10.4	< 10	—	0.78	0.36 to 1.70	5,527	17.9	< 10	—	0.50	0.20 to 1.24
Endocrine	2,419	7.8	< 10	—	0.34	0.08 to 1.38	2,947	9.5	< 10	—	1.19	0.51 to 2.78
Skin	5,648	18.3	23	20.7	1.38	0.85 to 2.24	5,394	17.5	18	16.2	1.21	0.63 to 2.32
Localized scleroderma	4,265	13.8	22	19.8	1.88	1.15 to 3.06	4,110	13.3	17	15.3	1.62	0.85 to 3.12
Gastrointestinal	3,458	11.2	10	9.0	1.15	0.59 to 2.24	6,043	19.5	15	13.5	1.42	0.77 to 2.64
Pernicious anemia	2,635	8.5	< 10	—	1.58	0.78 to 3.19	5,068	16.4	15	13.5	1.75	0.94 to 3.24
Nervous system	194	0.6	< 10	—	5.44	1.29 to 23.00	379	1.2	< 10	—	2.01	0.27 to 14.82
Asthma	4,338	14.0	< 10	—	0.92	0.45 to 1.86	5,133	16.6	13	11.7	1.75	0.89 to 3.44
Infections, by organ system												
Respiratory, upper airway	13,016	42.1	41	36.9	1.08	0.70 to 1.65	11,944	38.6	40	36.0	1.31	0.76 to 2.25
Otitis media	3,400	11.0	11	9.9	1.07	0.57 to 2.01	2,857	9.2	< 10	—	1.11	0.48 to 2.58
Pharyngitis	4,800	15.5	18	16.2	1.29	0.77 to 2.17	4,299	13	12	10.8	0.89	0.42-1.86
Sinusitis	9,109	29.5	30	27.0	1.12	0.72 to 1.74	8,120	26.3	26	23.4	1.09	0.59 to 2.01
Respiratory, lower airway	13,047	42.2	41	36.9	1.34	0.86 to 2.10	16,711	54.1	46	41.4	1.51	0.91 to 2.49
Acute bronchitis	9,819	31.8	30	27.0	1.14	0.73 to 1.79	9,358	30.3	27	24.3	1.17	0.67 to 2.07
Pneumonia	5,667	18.3	27	24.3	2.23	1.39 to 3.58	12,383	40.1	25	22.5	1.16	0.68 to 1.98
Skin	4,501	14.6	13	11.7	1.00	0.55 to 1.82	7,025	22.7	15	13.5	1.01	0.56 to 1.81
Cellulitis	2,465	8.0	< 10	—	0.59	0.28 to 1.70	3,762	12.2	11	9.9	1.59	0.84 to 3.01
Urinary tract	14,162	45.8	53	47.8	1.57	1.02 to 2.44	17,462	56.5	54	48.7	1.33	0.76 to 2.32
Cystitis/pyelonephritis, UTI	12,837	41.5	39	35.1	1.32	0.84 to 2.07	16,759	54.2	51	46.0	1.66	1.00 to 2.73
Prostatitis§	3,168	21.8	19	25.0	1.20	0.70 to 2.06	2,154	14.9	< 10	—	0.65	0.23 to 1.85

(continued on following page)

Table 2. Risk of Melanoma After First Primary NHL, by Subtype, in Relation to Autoimmune Conditions and Infections (continued)

	Before NHL Diagnosis						After NHL Diagnosis*					
	Total NHL		Melanoma Cases				Total NHL		Melanoma Cases			
Medical Conditions	No.	%	No.	%	HR†	95% CI	No.	%	No.	%	HR†	95% CI
Gastrohepatic	4,880	15.8	14	12.6	1.18	0.66 to 2.11	5,926	19.2	21	18.9	2.17	1.28 to 3.69
Gastroenteritis	4,689	15.2	13	11.7	1.11	0.61 to 2.03	5,556	18.0	19	17.1	1.91	1.10 to 3.33

NOTE. Counts and percentages are not reported for fewer than 10 melanoma cases to protect patient confidentiality.
Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; HR, hazard ratio; NHL, non-Hodgkin lymphoma; UTI, urinary tract infection.
*New claims occurring after NHL but before second cancer, death, end of study, or loss to follow-up, with no claims before NHL.
†Individuals with no history of the condition of interest comprise the referent group for each analysis. Hematologic autoimmune conditions (eg, autoimmune hemolytic anemia, thrombocytopenia) were excluded from consideration because of difficulty distinguishing these diagnoses from manifestations of chemotherapy toxicity. HR (95% CI) adjusted for sex, race, residence, Charlson comorbidity index, socioeconomic status, and follow-up time (time-dependent covariate) and stratified by calendar year. Age was used as the time scale.
‡B-cell activating conditions include rheumatoid arthritis, Sjogren's syndrome, discoid lupus erythematosus, reactive arthritis, Felty's syndrome, chronic thryoiditis, systemic/discoid lupus erythematosus, pernicious anemia, and myasthenia gravis. T-cell–activating conditions include ankylosing spondylitis, dermatomyositis, polymyalgia rheumatica, sarcoidosis, systemic sclerosis, rheumatic fever, chronic rheumatic heart disease, giant cell arteritis, systemic vasculitis, Addison's disease, Graves' disease, primary biliary cirrhosis, alopecia areata, localized scleroderma, dermatitis herpetiformis, psoriasis, celiac disease, Crohn's disease, ulcerative colitis, amyotrophic sclerosis, multiple sclerosis, and asthma.
§Among males only.

rituximab-, fludarabine-, or cyclophosphamide-containing chemotherapy (model A), or after radiotherapy (model B). In more detailed models, nonsignificant increased risks were observed among patients who received cyclophosphamide-containing chemotherapy without rituximab (model B; HR, 1.78; 95% CI, 0.97 to 3.25). These risks were particularly increased among individuals who also received doxorubicin (cyclophosphamide and doxorubicin without rituximab: n = 20; HR, 2.09; 95% CI, 1.11 to 3.92; cyclophosphamide without doxorubicin/rituximab: n = 4; HR, 1.01; 95% CI, 0.34 to 3.00).

T-cell–activating autoimmune diseases diagnosed before and after CLL/SLL were associated with significant increased risk of melanoma when compared with patients without T-cell–activating autoimmune diseases (before CLL/SLL: HR, 2.27; 95% CI, 1.34 to 3.84; after CLL/SLL: HR, 2.92; 95% CI, 1.66 to 5.12), whereas nonsignificant decreases in melanoma risk were observed for B-cell–activating conditions occurring before and after CLL/SLL (Table 2). Among T-cell–activating autoimmune conditions, risk of developing melanoma was particularly increased for individuals diagnosed before CLL/SLL with Graves' disease (HR, 2.66; 95% CI, 1.20 to 5.91) or psoriasis (HR, 2.68; 95% CI, 1.21 to 5.91), and after CLL/SLL diagnosis with chronic rheumatic heart disease (HR, 2.31; 95% CI, 1.23 to 4.36), skin-related autoimmune conditions (HR, 1.87; 95% CI, 1.02 to 3.43), and before and after CLL/SLL with asthma (before CLL/SLL: HR, 2.14; 95% CI, 1.13 to 4.02; after CLL/SLL: HR, 3.24; 95% CI, 1.75 to 6.00). Despite numerous infections diagnosed among patients with CLL/SLL, only cellulitis diagnosed before CLL/SLL (HR, 1.95; 95% CI, 1.02 to 3.74) and cystitis/pyelonephritis urinary tract infections diagnosed before and after CLL/SLL were associated with significantly elevated melanoma risk (before CLL/SLL: HR, 1.81; 95% CI, 1.08 to 3.01; after CLL/SLL: HR, 2.17; 95% CI, 1.24 to 3.78).

In contrast to CLL/SLL, among patients without CLL/SLL, diagnosis of B-cell– or T-cell–activating autoimmune conditions was not significantly related to subsequent melanoma risk (Table 2). In detailed analyses, the occurrence of localized scleroderma (T-cell–activating condition) before non-CLL/SLL diagnosis was associated with an increased melanoma risk (HR, 1.88; 95% CI, 1.15 to 3.06) and nervous system autoimmune conditions (HR, 5.44; 95% CI, 1.29 to 23.00). Among infections, melanoma risk was linked to pneumonia (HR, 2.23; 95% CI, 1.39 to 3.58) and urinary tract infections (HR, 1.57; 95% CI, 1.02 to 2.44) diagnosed before non-CLL/SLL and after non-CLL/SLL with gastrohepatic infections (mainly gastroenteritis; HR, 1.91; 95% CI, 1.10 to 3.33) and cystitis/pyelonephritis urinary tract infections (HR, 1.66; 95% CI, 1.00 to 2.73). Significant decreases in melanoma risk were not observed for any specific autoimmune conditions or infections.

Risk estimates for the associations described above were materially unchanged in multivariable analyses that included all chemotherapeutic agents as well as autoimmune conditions and infections with $P < .05$ in the same model. Risk estimates also were similar for melanomas less than 1-mm thick and 1-mm thick or greater, regardless of residence, and for DLBCL and FL survivors, although our sample size was limited for subgroup analyses.

Cumulative incidence of melanoma was higher for survivors of CLL/SLL than for survivors of non-CLL/SLL (1.37% *v* 0.78%, attained at age 85 years; Fig 1). Among survivors of CLL/SLL, the cumulative incidence of melanoma was higher for patients who received fludarabine-containing chemotherapy versus those who did not (1.66% *v* 1.22%), and for those with a diagnosis of T-cell–activating autoimmune conditions (1.64% *v* 1.03%).

DISCUSSION

In a large-scale, population-based study, we show, for the first time, to our knowledge, that patients with CLL/SLL who were treated with fludarabine-containing chemotherapy (with or without rituximab) or who were diagnosed with T-cell–activating autoimmune conditions have an approximately two-fold increased risk of developing cutaneous melanoma. In contrast, survivors of non-CLL/SLL had no evidence of heighted melanoma risk associated with either T-cell or B-cell autoimmune diseases, and specific chemotherapy regimens did not seem to strongly increase the risk of melanoma. In general, most infections did not seem to be related to melanoma risks. Our study results provide direct evidence for

Table 3. Risk of Melanoma After First Primary NHL, by Subtype, in Relation to NHL Treatments

NHL Treatment	Total NHL		Melanoma Cases			
	No.	%	No.	%	HR*	95% CI
Patients diagnosed with first primary CLL/SLL						
Infused chemotherapy						
None recorded	8,899	63.8	52	57.1	1.00	Referent
Model A†						
Any rituximab	3,744	26.8	27	29.7	1.43	0.77 to 2.67
Any fludarabine	2,958	21.2	28	30.8	1.90	1.08 to 3.37
Any cyclophosphamide	2,402	17.2	19	20.9	1.11	0.59 to 2.08
Model B‡						
Fludarabine without rituximab	917	6.6	10	11.0	2.92	1.42 to 6.01
Rituximab without fludarabine	1,703	12.2	< 10	—	1.63	0.79 to 3.38
Fludarabine + rituximab	2,041	14.6	18	19.8	1.92	1.09 to 3.40
Radiotherapy						
No	12,925	92.7	85	93.6	1.00	Referent
Yes	1,025	7.3	< 10	—	0.86	0.31 to 2.40
Patients diagnosed with first primary NHL other than CLL/SLL						
Infused chemotherapy						
None recorded	10,040	32.5	34	30.6	1.00	Referent
Model A†						
Any rituximab	15,726	50.9	53	47.8	1.06	0.62 to 1.84
Any fludarabine	2,518	8.1	< 10	—	1.22	0.57 to 2.61
Any cyclophosphamide	16,786	54.3	68	61.3	1.44	0.89 to 2.35
Model B‡						
Cyclophosphamide without rituximab	4781	15.5	24	21.6	1.78	0.97 to 3.25
Rituximab without cyclophosphamide	3,721	12.0	< 10	—	0.99	0.45 to 2.19
Cyclophosphamide + rituximab	12,005	38.8	44	39.6	1.27	0.77 to 2.12
Radiotherapy						
No	21,051	68.1	76	68.5	1.00	Referent
Yes	9,869	31.9	35	31.5	1.11	0.73 to 1.69

NOTE. Treatments received by fewer than 10 melanoma cases are not reported here but are included in Appendix Table 1 (eg, other alkylating agents, epipodophyllotoxins, and hematopoietic stem cell transplantation). Counts and percentages are not reported for fewer than 10 melanoma cases to protect patient confidentiality.

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; HR, hazard ratio; NHL, non-Hodgkin lymphoma.

*HR (95% CI) adjusted for sex, race, residence, Charlson comorbidity index, socioeconomic status, and follow-up time (time-dependent covariate) and stratified by calendar year. Age was used as the time scale. Time-dependent covariates were used to indicate receipt of any radiotherapy or chemotherapy during follow-up on the basis of timing of initiation of therapy. Model A represents risk for patients who received any of the three main chemotherapy agents with separate indicator variables for each agent. The categories in model B are mutually exclusive. The HRs for chemotherapy in models A and B were additionally adjusted for receipt of other alkylating agents. The HR for radiotherapy was additionally adjusted for chemotherapy using model B.

†Percentages do not add up to 100% because groups are not mutually exclusive.

‡Percentages do not add up to 100% because a small number of patients received other agents.

the importance of immune perturbation in explaining the excess of melanoma diagnoses observed in survivors of CLL/SLL.

Patients with CLL/SLL experience profound and prolonged immune dysfunction characterized by defective B-cell and T-cell function, which contributes to increased incidence of infections and autoimmune diseases.[44-46] In the first quantification of second melanoma risk associated with specific infused chemotherapy agents administered for CLL/SLL, including both initial and subsequent chemotherapy, we demonstrated that fludarabine-containing regimens, with or without rituximab, are linked to a significant excess risk of melanoma after CLL/SLL. Increased secondary malignancy risks, including treatment-related acute myeloid leukemia and solid malignancies, particularly skin cancers, have been reported in fludarabine-treated CLL/SLL cohorts,[9,13,47-53] but no previous study has directly compared melanoma risks in patients treated with and without fludarabine. The exact mechanism of action of fludarabine in the induction of cutaneous melanoma is unclear, but may be a result of inherent predisposition to malignancy among patients with CLL/SLL coupled with the immunosuppressive and DNA-damaging effects of fludarabine.[47,54,55]

Increased melanoma risks also have been observed in other immunosuppressed populations, such as solid organ and bone marrow transplant recipients, particularly those who received T-cell–depleting therapies,[23,26] as well as in persons with HIV/AIDS.[22,56] In addition, the critical role of T cells in the antitumor response in patients with melanoma is supported by the effectiveness of immunotherapy directed at T-cell checkpoints in treating metastatic melanoma.[57-59] In our study, the melanomas occurring after CLL/SLL were more likely to be 1-mm thick or greater compared with those occurring after other NHLs, which is consistent with previous studies reporting these melanomas as more advanced and more aggressive than melanomas that arise in the general population (Robbins et al, submitted for publication.[3,25,60-62] Patients with CLL/SLL are commonly diagnosed with hematologic autoimmune conditions (eg, autoimmune hemolytic anemia or thrombocytopenia); however, nonhematologic autoimmune diseases are reportedly rare (Robbins et al, submitted for

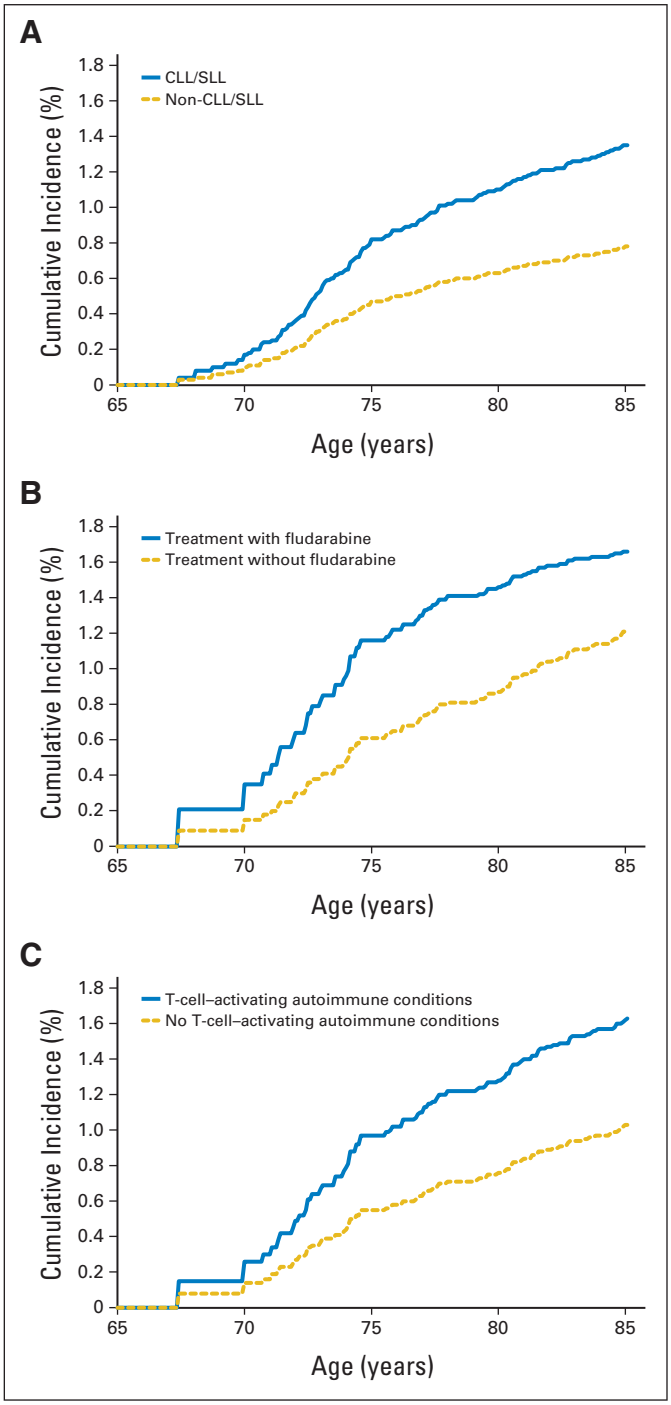

Fig 1. (A) Cumulative incidence of subsequent melanoma after non-Hodgkin lymphoma by subtype, (B) by fludarabine treatment among chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) survivors, and (C) by diagnosis of T-cell–activating autoimmune conditions among CLL/SLL survivors.

publication).[62] In a new finding, to our knowledge, we show that melanoma risk is approximately two-fold increased for patients with T-cell–activating autoimmune conditions, including Graves' disease, psoriasis, chronic rheumatic heart disease, localized scleroderma/psoriasis, and asthma. Combined with previous literature, our findings support the importance of T-cell dysfunction as a contributor to melanoma risk after CLL/SLL.

Although cutaneous melanoma has been reported in excess after all NHLs combined in numerous studies,[3-21] limited data by NHL subtype have suggested a modestly increased risk of melanoma after FL, whereas risk after DLBCL did not exceed unity.[3] In contrast to our CLL/SLL results, we found no significant associations between melanoma risk and treatment for non-CLL/SLL NHL subtypes, although a 70% nonsignificant increase in risk was seen among patients treated with cyclophosphamide-based regimens without rituximab. Although cyclophosphamide has been associated with immunosuppression at higher doses and can increase the risk of bacterial infections, the association is because of ensuing neutropenia and not reduced T-cell function.[63-65] Our investigation had relatively few melanoma cases after specific NHLs other than CLL/SLL; thus, future studies with larger numbers will be needed to evaluate treatment- and immune-related risk factors for non-CLL/SLL NHL.

We found little evidence that T-cell– or B-cell–activating autoimmune conditions were related to melanoma after non-CLL/SLL NHL, raising the possibility that these conditions may only contribute to the development of melanoma after NHL in the context of profound and prolonged immunosuppression, such as that seen after CLL/SLL. As the single exception, melanoma risk was significantly increased among individuals who developed localized scleroderma before NHL. We also observed increased risk for melanoma among individuals diagnosed with pneumonia, urinary tract infections, and gastrohepatic infections after non-CLL/SLL NHL, a different pattern of infections than that observed for survivors of CLL/SLL in whom melanoma risk was significantly associated with cellulitis and urinary tract infections. Although it is plausible that these infections could be markers of immune perturbation, and T-cell dysfunction, in particular, for pneumonia,[66,67] our data overall did not demonstrate strong associations with the occurrence of infections.

The primary strength of this study was analysis of a large, population-based cohort to identify specific risk factors for second melanoma development by NHL subtype, considering detailed treatment and nontreatment risk factors. The cohort, records-based study design also provided long-term follow-up for exposure assessment and second melanoma occurrence, and eliminated selection bias.

Despite these strengths, several key limitations should be considered in the interpretation of our results. Most notable, we lacked data on dose and duration of chemotherapy, and information on oral chemotherapy agents was not available for the duration of follow-up; thus, we could not ascertain receipt of chlorambucil or other oral alkylators.[49] Chlorambucil is myelosuppressive but does not typically result in profound T-cell depletion; nevertheless, our fludarabine-related risk estimates are likely to be conservative because patients who received only oral chemotherapy are included in our referent group.

In addition, because of the nature of the Medicare claims database, some exposures may have been misclassified (eg, because of missing information on infections and autoimmune diseases diagnosed in patients before enrollment into Medicare, or for mild infections for which the patient did not seek medical care). Because we did not include persons younger than 65 years at NHL diagnosis, our study findings may not be generalizable to younger populations. We also were restricted to assessing potential risk factors that generate a medical claim, excluding key melanoma risk factors, such as genetic susceptibility or a direct measure of sun exposure. However, our

analyses were adjusted for residence (a proxy for sun exposure), although this risk prediction model of melanoma incidence has not been validated in a cancer survivor population.[39]

We provide, to our knowledge, the first evidence that specific chemotherapeutic agents and immune-related medical conditions are related to subsequent melanoma risk among older survivors of CLL/SLL, but not among patients with other NHL subtypes combined. Our findings identify high-risk survivors of NHL who may benefit most from regular full skin examinations to maximize opportunities for early detection of cutaneous melanoma. Further research is needed to understand the biologic mechanisms behind the immune perturbations that lead to melanoma development and to determine if similar risks extend to younger survivors of NHL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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REFERENCES

1. Howlader N, Noone A, Krapcho M, et al: SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2011/
2. de Moor JS, Mariotto AB, Parry C, et al: Cancer survivors in the United States: Prevalence across the survivorship trajectory and implications for care. Cancer Epidemiol Biomarkers Prev 22:561-570, 2013
3. Morton LM, Curtis RE, Linet MS, et al: Second malignancy risks after non-Hodgkin's lymphoma and chronic lymphocytic leukemia: Differences by lymphoma subtype. J Clin Oncol 28:4935-4944, 2010
4. Travis LB, Curtis RE, Hankey BF, et al: Second cancers in patients with chronic lymphocytic leukemia. J Natl Cancer Inst 84:1422-1427, 1992
5. Goggins WB, Finkelstein DM, Tsao H: Evidence for an association between cutaneous melanoma and non-Hodgkin lymphoma. Cancer 91:874-880, 2001
6. Brennan P, Scelo G, Hemminki K, et al: Second primary cancers among 109,000 cases of non-Hodgkin's lymphoma. Br J Cancer 93:159-166, 2005
7. Tward JD, Wendland MMM, Shrieve DC, et al: The risk of secondary malignancies over 30 years after the treatment of non-Hodgkin lymphoma. Cancer 107:108-115, 2006
8. 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
9. Tsimberidou AM, Wen S, McLaughlin P, et al: Other malignancies in chronic lymphocytic leukemia/small lymphocytic lymphoma. J Clin Oncol 27:904-910, 2009
10. Pirani M, Marcheselli R, Marcheselli L, et al: Risk for second malignancies in non-Hodgkin's lymphoma survivors: A meta-analysis. Ann Oncol 22:1845-1858, 2011
11. Xu Y, Wang H, Zhou S, et al: Risk of second malignant neoplasms after cyclophosphamide-based chemotherapy with or without radiotherapy for non-Hodgkin lymphoma. Leuk Lymphoma 54:1396-1404, 2013
12. Hisada M, Biggar RJ, Greene MH, et al: Solid tumors after chronic lymphocytic leukemia. Blood 98:1979-1981, 2001
13. 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
14. Schollkopf C, Rosendahl D, Rostgaard K, et al: Risk of second cancer after chronic lymphocytic leukemia. Int J Cancer 121:151-156, 2007
15. Travis LB, Curtis RE, Boice JD Jr, et al: Second cancers following non-Hodgkin's lymphoma. Cancer 67:2002-2009, 1991
16. Travis LB, Curtis RE, Glimelius B, et al: Second cancers among long-term survivors of non-Hodgkin's lymphoma. J Natl Cancer Inst 85:1932-1937, 1993
17. Ellis M, Lishner M: Second malignancies following treatment in non-Hodgkin's lymphoma. Leuk Lymphoma 9:337-342, 1993
18. Dong C, Hemminki K: Second primary neoplasms among 53,159 haematolymphoproliferative malignancy patients in Sweden, 1958-1996: a search for common mechanisms. Br J Cancer 85:997-1005, 2001
19. 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
20. Royle JS, Baade P, Joske D, et al: Risk of second cancer after lymphohematopoietic neoplasm. Int J Cancer 129:910-919, 2011
21. Royle JA, Baade PD, Joske D, et al: Second cancer incidence and cancer mortality among chronic lymphocytic leukaemia patients: A population-based study. Br J Cancer 105:1076-1081, 2011
22. 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
23. Rizzo JD, Curtis RE, Socie G, et al: Solid cancers after allogeneic hematopoietic cell transplantation. Blood 113:1175-1183, 2009
24. Hemminki K, Jiang Y, Steineck G: Skin cancer and non-Hodgkin's lymphoma as second malignancies: Markers of impaired immune function? Eur J Cancer 39:223-229, 2003
25. Levi F, Randimbison L, Te VC, et al: Non-Hodgkin's lymphomas, chronic lymphocytic leukaemias and skin cancers. Br J Cancer 74:1847-1850, 1996
26. Engels EA, Pfeiffer RM, Fraumeni JF, et al: Spectrum of cancer risk among US solid organ transplant recipients. JAMA 306:1891-1901, 2011
27. Greene MH, Young TI, Clark WH Jr: Malignant melanoma in renal-transplant recipients. Lancet 1:1196-1199, 1981
28. Warren JL, Klabunde CN, Schrag D, et al: Overview of the SEER-Medicare data: Content, research applications, and generalizability to the United States elderly population. Med Care 40:IV3-IV18, 2002
29. World Health Organization: International Classification of Diseases for Oncology (ed 3). http://www.who.int/classifications/icd/adaptations/oncology/en/
30. Morton LM, Turner JJ, Cerhan JR, et al: Proposed classification of lymphoid neoplasms for epidemiologic research from the International Lymphoma Epidemiology Consortium (InterLymph). Blood 110:695-708, 2007
31. Swerdlow SH, Campo E, Harris NL, et al: World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France, IARC Press, 2008
32. Curtis RE, Freedman DM, Ron E, et al: New malignancies among cancer survivors: SEER Cancer Registries, 1973-2000. Bethesda, MD, National Cancer Institute, NIH publication 05-5302, 2006
33. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 17 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2009 Sub (1973-2007 varying), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2010, based on the November 2009 submission, 2010
34. Smedby KE, 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
35. Ballotti S, Chiarelli F, de Martino M: Autoimmunity: Basic mechanisms and implications in endocrine diseases—Part II. Horm Res 66:142-152, 2006
36. Sweet RA, Cullen JL, Shlomchik MJ: Rheumatoid factor B cell memory leads to rapid, switched antibody-forming cell responses. J Immunol 190:1974-1981, 2013
37. Zhang X, Ing S, Fraser A, et al: Follicular helper T cells: New insights into mechanisms of autoimmune diseases. Ochsner J 13:131-139, 2013
38. Porakishvili N, Mageed R, Jamin C, et al: Recent progress in the understanding of B-cell functions in autoimmunity. Scand J Immunol 54:30-38, 2001
39. Fears TR, Guerry IVD, Pfeiffer RM, et al: Identifying individuals at high risk of melanoma: A practical predictor of absolute risk. J Clin Oncol 24:3590-3596, 2006
40. Klabunde CN, Potosky AL, Jegler JM, et al: Development of a comorbidity index using physician claims data. J Clin Epidemiol 53:1258-1267, 2000

41. CLL Trialists' Collaborative Group: Chemotherapeutic options in chronic lymphocytic leukemia: A meta-analysis of the randomized trials. J Natl Cancer Inst 91:861-868, 1999

42. Baumert J, Schmidt M, Giehl KA, et al: Time trends in tumour thickness vary in subgroups: Analysis of 6475 patients by age, tumour site and melanoma subtype. Melanoma Res 19:24-30, 2009

43. Gooley TA, Leisenring W, Crowley J, et al: Estimation of failure probabilities in the presence of competing risks: New representations of old estimators. Stat Med 18:695-706, 1999

44. Riches JC, Gribben JG: Immunomodulation and immune reconstitution in chronic lymphocytic leukemia. Semin Hematol 51:228-234, 2014

45. Dasanu CA: Intrinsic and treatment-related immune alterations in chronic lymphocytic leukaemia and their impact for clinical practice. Expert Opin Pharmacother 9:1481-1494, 2008

46. Molica S: Second neoplasms in chronic lymphocytic leukemia: Incidence and pathogenesis with emphasis on the role of different therapies. Leuk Lymphoma 46:49-54, 2005

47. Keating MJ, O'Brien S, Lerner S, et al: Long-term follow-up of patients with chronic lymphocytic leukemia (CLL) receiving fludarabine regimens as initial therapy. Blood 92:1165-1171, 1998

48. Laurenti L, Tarnani M, Chiusolo P, et al: Low incidence of secondary neoplasia after autotransplantation for lymphoproliferative disease: The role of pre-transplant therapy. Clin Transplant 22:191-199, 2008

49. Misgeld E, Germing U, Aul C, et al: Secondary myelodysplastic syndrome after fludarabine therapy of a low-grade non-Hodgkin's lymphoma. Leuk Res 25:95-98, 2001

50. 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

51. Tam CS, Seymour JF, Prince HM, et al: Treatment-related myelodysplasia following fludarabine combination chemotherapy. Haematologica 91: 1546-1550, 2006

52. Armitage JO, Carbone PP, Connors JM, et al: Treatment-related myelodysplasia and acute leukemia in non-Hodgkin's lymphoma patients. J Clin Oncol 21:897-906, 2003

53. Bowcock SJ, Rassam SM, Lim Z, et al: High incidence of therapy-related myelodysplasia and acute leukaemia in general haematology clinic patients treated with fludarabine and cyclophosphamide for indolent lymphoproliferative disorders. Br J Haematol 134:242-243, 2006

54. Lukenbill J, Kalaycio M: Fludarabine: A review of the clear benefits and potential harms. Leuk Res 37:986-994, 2013

55. Robak T, Lech-Maranda E, Korycka A, et al: Purine nucleoside analogs as immunosuppressive and antineoplastic agents: Mechanism of action and clinical activity. Curr Med Chem 13:3165-3189, 2006

56. Lanoy E, Dores GM, Madeleine MM, et al: Epidemiology of nonkeratinocytic skin cancers among persons with AIDS in the United States. AIDS 23:385-393, 2009

57. Brahmer JR, Tykodi SS, Chow LQ, et al: Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 366:2455-2465, 2012

58. Topalian SL, Hodi FS, Brahmer JR, et al: Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 366:2443-2454, 2012

59. Hodi FS, O'Day SJ, McDermott DF, et al: Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363:711-723, 2010

60. Brewer JD, Shanafelt TD, Otley CC, et al: Chronic lymphocytic leukemia is associated with decreased survival of patients with malignant melanoma and merkel cell carcinoma in a SEER population-based study. J Clin Oncol 30:843-849, 2012

61. Frankenthaler A, Sullivan RJ, Wang W, et al: Impact of concomitant immunosuppression on the presentation and prognosis of patients with melanoma. Melanoma Res 20:496-500, 2010

62. Farma JM, Zager JS, Barnica-elvir V, et al: A collision of diseases: Chronic lymphocytic leukemia discovered during lymph node biopsy for melanoma. Ann Surg Oncol 20:1360-1364, 2013

63. McCune WJ, Golbus J, Zeldes W, et al: Clinical and immunologic effects of monthly administration of intravenous cyclophosphamide in severe systemic lupus erythematosus. N Engl J Med 318: 1423-1431, 1998

64. Monach PA, Arnold LM, Merkel PA: Incidence and prevention of bladder toxicity from cyclophosphamide in the treatment of rheumatic diseases: A data-driven review. Arthritis Rheum 62:9-21, 2010

65. Pryor BD, Bologna SG, Kahl LE: Risk factors for serious infection during treatment with cyclophosphamide and high-dose corticosteroids for systemic lupus erythematosus. Arthritis Rheum 39: 1475-1482, 1996

66. Lu YJ, Gross J, Bogaert D, et al: Interleukin-17A mediates acquired immunity to pneumococcal colonization. PLoS Pathog 4:e10000159, 2008

67. Zhang Z, Clarke TB, Weiser JN: Cellular effectors mediate Th17-dependent clearance of pneumococcal colonization in mice. J Clin Invest 119:1899-1909, 2009

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Risk Factors for Melanoma Among Survivors of Non-Hodgkin Lymphoma

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Appendix

Table A1. Frequency of Receipt and Medical Claim Codes for Specific Chemotherapeutic Agents

Chemotherapy	HCPCS/CPT Codes	Total NHL		Melanoma Cases*	
		No.	%	No.	%
Patients diagnosed with first primary CLL/SLL					
Most common agents					
Cyclophosphamide	J8530, J9070, J9080, J9090-J9097	2,402	17.2	19	20.9
Fludarabine	J9185	2,958	21.2	28	30.8
Rituximab	J9310	3,744	26.8	27	29.7
Plant alkaloids					
Vincristine	J9370, J9375, J9380	1,590	11.4	13	14.3
Patients diagnosed with first primary NHL other than CLL/SLL					
Most common agents					
Cyclophosphamide	J8530, J9070, J9080, J9090-J9097	16,786	54.3	68	61.3
Rituximab	J9310	15,726	50.9	53	47.8
Topoisomerases II inhibitors					
Doxorubicin	J9000-J9001	12,115	39.2	56	50.5
Plant alkaloids					
Vincristine	J9370, J9375, J9380	16,365	52.9	63	56.8
Colony stimulating factors					
G-CSF	J1440-J1441	7,027	22.7	26	23.4

NOTE. Information on oral chemotherapy agents not captured in study include capecitabine, chlorambucil, cyclophosphamide, levamisole, procarbazine, and temozolomide.

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CPT, Current Procedural Technology; G-CSF, granulocyte colony-stimulating factor; HCPCS, Health Care Common Procedure Coding System; NHL, non-Hodgkin lymphoma.

*Counts and percentages are not reported when fewer than 10 melanoma cases to protect patient confidentiality. Chemotherapy agents with fewer than 10 melanoma cases include aldesleukin, alemtuzumab, idarubicin, ixabepilone, asparaginase, azacitidine, bendamustine, bevacizumab, bleomycin, bortezomib, busulfan, carboplatin, carmustine, cetuximab, cisplatin, cladribine, clofarabine, cytarabine, dacarbazine, dactinomycin, daunorubicin, decitabine, denileukin, diftitox, docetaxel, epirubicin, etoposide, floxuridine, fluorouracil, gefitinib, gemcitabine, gemtuzumab, G-CSF, ibritumomab, ifosfamide, interferons (1B, 2A, 2B, A1, N3), irinotecan, leucovorin, lomustine, mechlorethamine, melphalan, methotrexate, mitomycin, mitoxantrone, nelarabine, oxaliplatin, paclitaxel, panitumumab, pegaspargase, pemetrexed, pentostatin, plicamycin, streptozocin, temsirolimus, teniposide, thiotepa, topotecan, tositumomab, trastuzumab, valrubicin, vinblastine, and vinorelbine.

Table A2. Frequency of Diagnosis and Medical Claim Codes for Autoimmune Conditions

Autoimmune Conditions	HCPCS/CPT Codes	Total NHL				Melanoma Cases			
		Before NHL		After NHL*		Before NHL		After NHL*	
		No.	%	No.	%	No.	%	No.	%
Patients diagnosed with first primary CLL/SLL									
B-cell–activating conditions†	Conditions below	2,263	16.2	3,637	26.1	< 10	—	13	14.3
T-cell–activating conditions†	Conditions below	5,488	39.3	6,749	48.4	36	39.6	49	53.9
By organ system involved									
Systemic/connective tissue		1,687	12.1	1,912	13.7	< 10	—	< 10	—
Ankylosing spondylitis	720	321	2.3	377	2.7	< 10	—	< 10	—
Dermatomyositis/polymyositis	710.3, 710.4	37	0.3	39	0.3	< 10	—	< 10	—
Felty's syndrome	714.1	15	0.1	15	0.1	< 10	—	< 10	—
Systemic lupus erythematosus	710	348	2.5	424	3.0	< 10	—	< 10	—
Polymyalgia rheumatica	725	256	1.8	295	2.1	< 10	—	< 10	—
Reactive arthritis	99.3	< 10	—	< 10	—	< 10	—	< 10	—
Rheumatic fever	390-392	46	0.3	52	0.4	< 10	—	< 10	—
Rheumatoid arthritis	714	981	7.0	1,037	7.4	< 10	—	< 10	—
Sarcoidosis	135	35	0.3	43	0.3	< 10	—	< 10	—
Sjogren's syndrome	710.2	123	0.9	128	0.9	< 10	—	< 10	—
Systemic sclerosis/scleroderma	710.1	17	0.1	24	0.2	< 10	—	< 10	—
Cardiovascular		1,367	9.8	2,370	17.0	< 10	—	15	16.5
Chronic rheumatic heart disease	393-398	1,219	8.7	2,187	15.7	< 10	—	15	16.5
Giant cell arteritis	446.5	127	0.9	134	1.0	< 10	—	< 10	—
Systemic vasculitis	446,447.60	174	1.3	239	1.7	< 10	—	< 10	—
Endocrine		931	6.7	1,213	8.7	< 10	—	< 10	—
Addison's disease	255.4	71	0.5	242	1.7	< 10	—	< 10	—
Chronic thyroiditis/Hashimoto thyroiditis	245.2	103	0.7	134	1.0	< 10	—	< 10	—
Graves' disease	242	783	5.6	872	6.3	< 10	—	< 10	—
Primary biliary cirrhosis	571.6	12	0.1	23	0.2	< 10	—	< 10	—
Skin		2,222	15.9	2,402	17.2	18	19.8	21	23.1
Alopecia areata	704.1	25	0.2	55	0.4	< 10	—	< 10	—
Dermatitis herpetiformis	694	56	0.4	114	0.8	< 10	—	< 10	—
Discoid lupus erythematosus	695.4	34	0.2	38	0.3	< 10	—	< 10	—
Localized scleroderma	701	1,809	13.0	1,924	13.8	12	13.2	13	14.3
Psoriasis	696	445	3.2	431	3.1	< 10	—	< 10	—
Gastrointestinal		1,435	10.3	2,926	21.0	< 10	—	< 10	—
Celiac disease	579	149	1.1	203	1.5	< 10	—	< 10	—
Crohn's disease	555	105	0.8	142	1.0	< 10	—	< 10	—
Pernicious anemia	281	1,119	8.0	2,548	18.3	< 10	—	< 10	—
Ulcerative colitis	556	187	1.3	255	1.8	< 10	—	< 10	—
Nervous system		110	0.8	180	1.3	< 10	—	< 10	—
Amyotrophic sclerosis	335.2	10	0.1	48	0.3	< 10	—	< 10	—
Multiple sclerosis	340	54	0.4	69	0.5	< 10	—	< 10	—
Myasthenia gravis	358	50	0.4	69	0.5	< 10	—	< 10	—
Respiratory (asthma)	493	1,919	13.8	2,484	17.8	13	14.3	18	19.8
Autoimmune disease, NOS	279.4	32	0.23	64	0.5	< 10	—	< 10	—
Patients diagnosed with first primary NHL other than CLL/SLL									
B-cell–activating conditions †	Conditions below	6,013	19.5	8,078	26.1	16	14.4	24	21.6
T-cell–activating conditions †	Conditions below	13,142	42.5	15,201	49.2	36	32.4	35	31.5
By organ system involved									
Systemic/connective tissue		4,798	15.5	4,734	15.3	< 10	—	< 10	—
Ankylosing spondylitis	720	790	2.6	853	2.8	< 10	—	< 10	—
Dermatomyositis/polymyositis	710.3, 710.4	126	0.4	113	0.4	< 10	—	< 10	—
Felty's syndrome	714.1	32	0.1	31	0.1	< 10	—	< 10	—
Systemic lupus erythematosus	710	1,146	3.7	1,189	3.9	< 10	—	< 10	—
Polymyalgia rheumatica	725	727	2.4	671	2.2	< 10	—	< 10	—
Reactive arthritis	99.3	12	0.0	< 10	—	< 10	—	< 10	—
Rheumatic fever	390-392	78	0.3	99	0.3	< 10	—	< 10	—

(continued on following page)

Table A2. Frequency of Diagnosis and Medical Claim Codes for Autoimmune Conditions (continued)

Autoimmune Conditions	HCPCS/CPT Codes	Total NHL				Melanoma Cases			
		Before NHL		After NHL*		Before NHL		After NHL*	
		No.	%	No.	%	No.	%	No.	%
Rheumatoid arthritis	714	2,961	9.6	2,658	8.6	< 10	—	< 10	—
Sarcoidosis	135	144	0.5	180	0.6	< 10	—	< 10	—
Sjogren's syndrome	710.2	446	1.4	495	1.6	< 10	—	< 10	—
Systemic sclerosis/scleroderma	710.1	99	0.3	106	0.3	< 10	—	< 10	—
Cardiovascular		3,212	10.4	5,527	17.9	< 10	—	< 10	—
Chronic rheumatic heart disease	393-398	2,771	9.0	5,071	16.4	< 10	—	< 10	—
Giant cell arteritis	446.5	368	1.2	355	1.2	< 10	—	< 10	—
Systemic vasculitis	446,447.60	521	1.7	585	1.9	< 10	—	< 10	—
Endocrine		2,419	7.8	2,947	9.5	< 10	—	< 10	—
Addison's disease	255.4	146	0.5	586	1.9	< 10	—	< 10	—
Chronic thyroiditis/Hashimoto thyroiditis	245.2	307	1.0	441	1.4	< 10	—	< 10	—
Graves' disease	242	2,042	6.6	2,067	6.7	< 10	—	< 10	—
Primary biliary cirrhosis	571.6	34	0.1	56	0.2	< 10	—	< 10	—
Skin		5,648	18.3	5,394	17.5	23	20.7	18	16.2
Alopecia areata	704.1	47	0.2	50	0.2	< 10	—	< 10	—
Dermatitis herpetiformis	694	173	0.6	214	0.7	< 10	—	< 10	—
Discoid lupus erythematosus	695.4	151	0.5	135	0.4	< 10	—	< 10	—
Localized scleroderma	701	4,265	13.8	4,110	13.3	22	19.8	17	15.3
Psoriasis	696	1,465	4.7	1,357	4.4	< 10	—	< 10	—
GI		3,458	11.2	6,043	19.5	10	9.0	15	13.5
Celiac disease	579	364	1.2	507	1.6	< 10	—	< 10	—
Crohn's disease	555	291	0.9	372	1.2	< 10	—	< 10	—
Pernicious anemia	281	2,635	8.5	5,068	16.4	< 10	—	< 10	—
Ulcerative colitis	556	469	1.5	612	2.0	< 10	—	< 10	—
Nervous system		194	0.6	379	1.2	< 10	—	< 10	—
Amyotrophic sclerosis	335.2	30	0.1	77	0.3	< 10	—	< 10	—
Multiple sclerosis	340	69	0.2	145	0.5	< 10	—	< 10	—
Myasthenia gravis	358	102	0.3	163	0.5	< 10	—	< 10	—
Respiratory (asthma)	493	4,338	14.0	5,133	16.6	< 10	—	< 10	—
Autoimmune disease, NOS	279.4	120	0.4	161	0.5	< 10	—	< 10	—

NOTE. Counts and percentages are not reported for fewer than 10 melanoma cases to protect patient confidentiality.

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CPT, Current Procedural Technology; HCPCS, Health care Common Procedure Coding System; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified.

*New claims occurring after NHL but before second cancer, death, end of study, or loss to follow-up, with no claims before NHL.

†B-cell–activating conditions include rheumatoid arthritis, Sjogren's syndrome, discoid lupus erythematosus, reactive arthritis, Felty's syndrome, chronic thryoiditis, systemic/discoid lupus erythematosus, pernicious anemia, and myasthenia gravis. T-cell–activating conditions include ankylosing spondylitis, dermatomyositis, polymyalgia rheumatica, sarcoidosis, systemic sclerosis, rheumatic fever, chronic rheumatic heart disease, giant cell arteritis, systemic vasculitis, Addison's disease, Graves' disease, primary biliary cirrhosis, alopecia areata, localized scleroderma, dermatitis herpetiformis, psoriasis, celiac disease, Crohn's disease, ulcerative colitis, amyotrophic sclerosis, multiple sclerosis, and asthma. Hematologic autoimmune conditions (eg, autoimmune hemolytic anemia, thrombocytopenia) were excluded from consideration because of difficulty distinguishing these diagnoses from manifestations of chemotherapy toxicity.

Table A3. Frequency of Diagnosis and Medical Claim Codes for Infections

Infections	HCPCS/CPT Codes	Total NHL				Melanoma Cases			
		Before NHL		After NHL*		Before NHL		After NHL*	
		No.	%	No.	%	No.	%	No.	%
Patients diagnosed with first primary CLL/SLL									
Respiratory, upper airway		5,847	41.9	5,850	41.9	35	38.5	35	38.5
Laryngitis	464-464.4, 476-476.1	593	4.3	614	4.4	< 10	—	< 10	—
Otitis media	017.4, 055.2, 381.0-381.4, 382, 383.0-383.1	1,621	11.6	1,514	10.9	< 10	—	< 10	—
Pharyngitis	462,472.1	2,141	15.4	2,143	15.4	10	11.0	11	12.1
Sinusitis	461,473	4,074	29.2	4,238	30.4	24	26.4	29	31.9
Respiratory, lower airway		6,122	43.9	8,347	59.8	37	40.7	41	45.1
Acute bronchitis	466	4,526	32.4	5,081	36.4	27	29.7	34	37.4
Influenza	487	783	5.6	821	5.9	< 10	—	< 10	—
Pneumonia	480-486, 770	2,872	20.6	6,414	46.0	16	17.6	21	23.1
Tuberculosis	010-018	122	0.9	150	1.1	< 10	—	< 10	—
Skin		2,125	15.2	3,490	25.0	17	18.7	21	23.1
Cellulitis	682.9	1,191	8.5	1,948	14.0	11	12.1	11	12.1
Herpes zoster	53	1,079	7.7	1,958	14	< 10	—	13	14.3
Urinary tract		6,227	44.6	7,942	56.9	39	42.9	46	50.6
Cystitis/pyelonephritis, UTI	599	5,630	40.4	7,599	54.5	34	37.4	40	44.0
Prostatitis†	601	1,554	20.5	1,199	15.8	17	23.0	14	18.9
Gastrohepatic		2,084	14.9	2,594	18.6	11	12.1	12	13.2
Gastroenteritis	558.9	2,020	14.5	2,445	17.5	11	12.1	11	12.1
HBV	070.2-070.3	36	0.3	96	0.7	< 10	—	< 10	—
HCV	070.4, 070.5, 070.7	51	0.4	133	1.0	< 10	—	< 10	—
Patients diagnosed with first primary NHL other than CLL/SLL									
Respiratory, upper airway		13,016	42.1	11,944	38.6	41	36.9	40	36.0
Laryngitis	464-464.4, 476-476.1	1,467	4.7	1,390	4.5	< 10	—	< 10	—
Otitis media	017.4, 055.2, 381.0-381.4, 382, 383.0-383.1	3,400	11.0	2,857	9.2	11	9.9	< 10	—
Pharyngitis	462, 472.1	4,800	15.5	4,299	13	18	16.2	12	10.8
Sinusitis	461, 473	9,109	29.5	8,120	26.3	30	27.0	26	23.4
Respiratory, lower airway		13,047	42.2	16,711	54.1	41	36.9	46	41.4
Acute bronchitis	466	9,819	31.8	9,358	30.3	30	27.0	27	24.3
Influenza	487	1,707	5.5	1,531	5.0	< 10	—	< 10	—
Pneumonia	480-486, 770	5,667	18.3	12,383	40.1	27	24.3	25	22.5
Tuberculosis	010-018	315	1.0	454	1.5	< 10	—	< 10	—
Skin		4,501	14.6	7,025	22.7	13	11.7	15	13.5
Cellulitis	682.9	2,465	8.0	3,762	12.2	< 10	—	11	9.9
Herpes zoster	53	2,295	7.4	3,980	12.9	< 10	—	< 10	—
Urinary tract		14,162	45.8	17,462	56.5	53	47.8	54	48.7
Cystitis/pyelonephritis, UTI	599	12,837	41.5	16,759	54.2	39	35.1	51	46.0
Prostatitis†	601	3,168	21.8	2,154	14.9	19	25.0	< 10	—
Gastrohepatic		4,880	15.8	5,926	19.2	14	12.6	21	18.9
Gastroenteritis	558.9	4,689	15.2	5,556	18.0	13	11.7	19	17.1
HBV	070.2-070.3	95	0.3	198	0.6	< 10	—	< 10	—
HCV	070.4, 070.5, 070.7	196	0.6	336	1.1	< 10	—	< 10	—

NOTE. Counts and percentages are not reported for fewer than 10 melanoma cases to protect patient confidentiality.

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CPT, Current Procedural Technology; HCPCS, Health care Common Procedure Coding System; HBV, hepatitis B virus; HCV, hepatitis C virus; ICD, International Classification of Diseases; NHL, non-Hodgkin lymphoma; UTI, urinary tract infection.

*New claims occurring after NHL but before second cancer, death, end of study, or loss to follow-up, with no claims before NHL.

†Among males only.

Table A4. Risk of Melanoma After First Primary NHL, by Subtype

Variable	Total NHL				CLL/SLL				Other NHL Subtypes			
	No.	%	HR*	95% CI	No.	%	HR*	95% CI	No.	%	HR*	95% CI
Sex												
Male	22,097	49.3	1.00	Referent	7,590	54.4	1.00	Referent	14,507	46.9	1.00	Referent
Female	22,773	50.8	0.31	0.23 to 0.43	6,360	45.6	0.24	0.14 to 0.41	16,413	53.1	0.37	0.24 to 0.55
Race												
White	40,752	90.8	1.00	Referent	12,841	92.1	1.00	Referent	27,911	90.3	1.00	Referent
Other/unknown	4,118	9.2	0.36	0.16 to 0.81	1,109	7.9	0.17	0.02 to 1.20	3,009	9.7	0.46	0.19 to 1.14
Residence at time of NHL diagnosis†												
North	20,348	45.4	1.00	Referent	6,691	48.0	1.00	Referent	13,657	44.2	1.00	Referent
Central	12,778	28.5	0.98	0.68 to 1.39	3,727	26.7	1.19	0.70 to 2.00	9,051	29.3	0.88	0.54 to 1.42
South	11,744	26.2	1.38	1.00 to 1.92	3,532	25.3	1.40	0.85 to 2.29	8,212	26.6	1.36	0.88 to 2.11
Charlson comorbidity index												
No comorbidities	11,134	24.8	1.00	Referent	3,322	23.8	1.00	Referent	7,812	25.3	1.00	Referent
1 comorbidity	11,138	24.8	0.62	0.44 to 0.88	3,366	24.1	0.51	0.29 to 0.87	7,772	25.1	0.75	0.47 to 1.18
2+ comorbidities	22,473	50.1	0.36	0.26 to 0.50	7,226	51.8	0.33	0.20 to 0.54	15,247	49.3	0.40	0.25 to 0.63
Missing	125	0.3	2.34	0.57 to 9.62	36	0.3	2.59	0.34 to 19.63	89	0.3	2.47	0.33 to 18.58
Socioeconomic status												
Lowest quintile	9,832	21.9	1.00	Referent	3,239	23.2	1.00	Referent	6,593	21.3	1.00	Referent
2nd lowest quintile	9,792	21.8	1.17	0.72 to 1.92	3,087	22.1	1.27	0.60 to 2.65	6,705	21.7	1.13	0.58 to 2.19
Middle quintile	10,062	22.4	1.30	0.80 to 2.10	3,140	22.5	1.23	0.58 to 2.61	6,922	22.4	1.39	0.73 to 2.63
2nd highest quintile	9,295	20.7	1.52	0.95 to 2.44	2,742	19.7	1.59	0.78 to 3.27	6,553	21.2	1.47	0.78 to 2.78
Highest quintile	5,374	12.0	1.93	1.17 to 3.17	1,540	11.0	2.70	1.31 to 5.56	3,834	12.4	1.43	0.71 to 2.86
Missing	515	1.1	3.57	1.62 to 7.88	202	1.4	4.29	1.50 to 12.25	313	1.0	2.95	0.85 to 10.29
NHL subtype												
DLBCL	10,311	23.0	1.00	Referent								
CLL/SLL	13,950	31.1	1.65	1.11 to 2.45								
FL	7,437	16.6	1.25	0.78 to 2.01								
MZL	3,516	7.8	0.90	0.44 to 1.82								
Other	9,656	21.5	0.93	0.58 to 1.51								

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HR, hazard ratio; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma.

*The HRs (95% CI) were calculated using one model including indicator variables for sex, race, residence, Charlson comorbidity index, socioeconomic status, and NHL subtype, then adjusted for follow-up time and stratified by calendar year with age as the time scale.

†Residence defined by Surveillance, Epidemiology, and End Results registry areas, including north (Connecticut, Detroit, Iowa, Seattle, and New Jersey), central (San Francisco, Utah, San Jose, Greater California, and Kentucky), and south (Hawaii, New Mexico, Atlanta, Los Angeles, Rural Georgia, Greater Georgia, and Louisiana).