

## Prior medical conditions and medication use and risk of non-Hodgkin lymphoma in connecticut United States women

Yawei Zhang<sup>1</sup>, Theodore R. Holford<sup>1</sup>, Brian Leaderer<sup>1</sup>, Shelia Hoar Zahm<sup>2</sup>, Peter Boyle<sup>3</sup>, Lindsay McOmber Morton<sup>1</sup>, Bing Zhang<sup>4</sup>, Kaiyong Zou<sup>5</sup>, Stuart Flynn<sup>6</sup>, Giovanni Tallini<sup>6</sup>, Patricia H. Owens<sup>1</sup> & Tongzhang Zheng<sup>1,\*</sup>

<sup>1</sup>Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT 06520, USA;

<sup>2</sup>Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda, MD 20892, USA;

<sup>3</sup>Department of Epidemiology and Biostatistics, European Institute of Oncology, 20141 Milan, Italy; <sup>4</sup>Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada, H3A1A2; <sup>5</sup>Department of Molecular, Cellular and Developmental Biology, Yale University, New Haven, CT 06520, USA; <sup>6</sup>Department of Pathology, Yale University School of Medicine, New Haven, CT 06520, USA

Received 11 September 2003; accepted in revised form 19 February 2004

*Key words:* case-control studies, medical condition, medication, non-Hodgkin's lymphoma.

### Abstract

*Objective:* To further investigate the role of prior medical conditions and medication use in the etiology of non-Hodgkin lymphoma (NHL), we analyzed the data from a population-based case-control study of NHL in Connecticut women.

*Methods:* A total of 601 histologically confirmed incident cases of NHL and 717 population-based controls were included in this study. In-person interviews were administered using standardized, structured questionnaires to collect information on medical conditions and medication use.

*Results:* An increased risk was found among women who had a history of autoimmune disorders (such as rheumatoid arthritis, lupus erythematosus, Sjogren's syndrome, and multiple sclerosis), anemia, eczema, or psoriasis. An increased risk was also observed among women who had used steroidal anti-inflammatory drugs and tranquilizers. A reduced risk was found for women who had scarlet fever or who had used estrogen replacement therapy, aspirin, medications for non-insulin dependent diabetes, HMG-CoA reductase inhibitors, or beta-adrenergic blocking agents. Risk associated with past medical history appeared to vary based on NHL subtypes, but the results were based on small number of exposed subjects.

*Conclusion:* A relationship between certain prior medical conditions and medication use and risk of NHL was observed in this study. Further studies are warranted to confirm our findings.

### Introduction

The incidence of non-Hodgkin lymphoma (NHL) has been increasing in Connecticut and in many other parts of the world [1,2]. The risk factors responsible for the observed increase, however, are largely unknown. Various medical conditions (such as primary or acquired immunosuppression, autoimmune disorders, diabetes, skin conditions, and allergy [3–22]) and medications

(such as oral contraceptives, estrogen replacement therapy, anti-convulsant drugs, tranquilizers, antibiotics, aspirin, thyroid medication, various steroids, digitalis, and antacids [11, 13, 20, 23–29]) have been reported to increase the risk of NHL in epidemiologic studies. However, other than conditions or treatments associated with immune alterations, the results have been inconsistent. For example, eczema was linked to an increased risk of NHL in some studies [9–12], but not in another study [13]. Psoriasis was found to be associated with NHL risk in some studies [7, 14–16], but not in other studies [11, 17, 18]. Estrogen use was reported to increase NHL risk in two studies [13, 19], but not in two

\*Address correspondence to: T. Zheng, 129 Church Street, Suite 700, New Haven, CT 06510. Ph.: +1-203-785-2882; Fax: +1-203-764-9782; E-mail: tongzhang.zheng@yale.edu

other studies [20, 23]. Thus, further examination of the association between past medical history and NHL risk is clearly warranted.

While further study of medical history in NHL is warranted, it is also important to examine the risk of NHL by subtypes, in view of the etiologic heterogeneity of these tumors [30]. In this study, we analyzed the data from a large population based case-control study in Connecticut women.

## Materials and methods

### *Study population*

Incident NHL female cases aged 21–84 were identified and histologically confirmed (ICD-O, Second Edition (31), M-9590-9595, 9670-9687, 9690-9698, 9700-9723) in Connecticut. Subjects were restricted to women who had no previous diagnosis of cancer, with the exception of non-melanoma skin cancer, and who were alive at the time of interview. A total of 1122 potential cases diagnosed between January 1996 and June 2000 were identified through the Yale Cancer Center's Rapid Case Ascertainment Shared Resource (RCA), an agent of the Connecticut Tumor Registry (CTR). The Connecticut Public Health code requires reporting of cancers from licensed hospitals and clinical laboratories to the CTR. RCA field personnel are assigned geographically to survey all of the state's non-pediatric hospitals to identify newly diagnosed cases. Information on cases identified in the field is regularly sent to the RCA data entry staff, where the case's demographic data are entered, verified and screened against the CTR database. The CTR has reciprocal reporting agreements with cancer registries in all adjacent states and Florida to identify Connecticut residents with cancer diagnosed and/or treated in these states. Of these 1122 potential cases, 167 (15%) died before interview and 123 (11%) were ineligible due to previous diagnosis of cancer, unable speak English, or physician refusal. Of 832 eligible and living cases, 601 (72%) completed in-person interviews with a mean time between diagnosis and interview of three months.

To provide accurate and consistent histological classification of cases, pathology slides (or tissue blocks) were obtained for NHL cases from the pathology departments where the cases were diagnosed. Each specimen was independently reviewed by two study pathologists (Drs. Flynn and Tallini), who are experienced in the diagnosis of lymphoma. If there was disagreement between the two pathologists, they worked together until a consensus was reached. If a consensus

could not be reached, the subject was assigned as an unspecified NHL case. NHL cases were classified according to both Working Formulation and REAL classification systems [30]. The REAL classification system was used in this paper for NHL subtype analyses.

Population-based controls with Connecticut addresses were recruited using random digit dialing (RDD) methods for those below age 65, and Centers for Medicare and Medicaid Service (CMMS) files for those aged 65 and over. The participation rate was 69% for RDD controls, including the initial telephone screening, and 47% for CMMS controls. Cases and controls were frequency matched by age within five-year groups by adjusting the number of controls randomly selected in each age stratum every few months.

### *Interviews*

All procedures were performed in accordance with a protocol approved by Human Investigation Committees at Yale University, the Connecticut Department of Public Health, and the National Cancer Institute. After approval by the hospitals and by each subject's physician (for cases), or following selection through random sampling (for controls), potential participants were approached by letter and/or by phone. Subjects who agreed to participate were interviewed by trained study interviewers either at the subject's home or at a convenient location. A standardized, structured questionnaire was used to obtain information on medical history and other major known or suspected risk factors that might confound the association between prior medical conditions and medication use and risk of NHL.

Since current medical condition and/or medication use may reflect the preclinical manifestation of NHL, or part of the treatment of the symptoms caused by NHL, past medical conditions and medicine use data were restricted to those that occurred one year before diagnosis for cases or one year before interview for controls. Using a list of 36 medical conditions, subjects were asked whether they had been diagnosed with each condition by a physician prior to one year ago; if so, subjects were asked the year and age at which the condition was first diagnosed. An open-ended question was used to ask whether the subject had taken any medicine at least once a day for a period of six months or longer previous to one year ago. If yes, the age at first and last use, and the total months of use of the medicine were also ascertained.

During the interview, we collected information on other potential confounding factors, including family

history of cancer, diet, occupation, tobacco use, alcohol consumption, blood transfusion history, menopausal status, and demographic factors. Dietary information was collected using a scannable semi-quantitative food frequency questionnaire developed and validated at the Fred Hutchinson Cancer Research Center.

*Data analysis*

Prior medication use was categorized into groups based on the published literature. Duration of use for each medication group was divided into tertiles based on the distribution of controls. Unconditional logistic regression was used to estimate the association of prior medical condition and medication use with risk of NHL overall and by histological type, immunologic type, and tumor grade. Potential confounding variables included in the final model were age, body mass index (BMI), menopausal status, and family history of NHL in first-degree relatives. Adjustment of other variables, such as

race, education, tobacco use, or alcohol consumption, did not result in material change of the observed associations, and thus were not included in the final model. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using SAS statistical software.

**Results**

Table 1 presents the distribution of selected characteristics for cases and controls. More cases reported a family history of NHL and higher BMI than controls. Controls, on the other hand, had a slightly higher level of education and alcohol intake than cases. No other factors showed a material difference between the cases and controls.

Table 2 presents selected prior medical conditions and risk of NHL. Autoimmune disorders as a group were associated with significantly increased risk of NHL (OR: 2.2, 95% CI: 1.3, 3.7). Women with anemia also

Table 1. Selected baseline characteristics of NHL cases and controls among Connecticut women

	Cases		Controls	
	n	%	n	%
<i>Age (years)</i>				
<50	119	19.8	155	21.6
50–70	277	46.1	317	44.2
>70	205	34.1	245	34.2
<i>Race</i>				
White	571	95.0	667	93.0
Black	18	3.0	25	3.5
Others	12	2.0	25	3.5
<i>Family history of NHL</i>				
No	592	98.5	713	99.4
Yes	9	1.5	4	0.6
<i>Tobacco smoking</i>				
No	270	44.9	323	45.0
Yes	331	55.1	394	55.0
<i>Alcohol drinking</i>				
No	230	38.2	233	32.5
Yes	371	61.8	484	67.5
<i>Education level</i>				
High school or less	261	43.4	265	37.0
College or higher	340	56.6	452	63.0
<i>BMI (kg/m<sup>2</sup>)</i>				
<25	298	49.6	404	56.4
25–29.99	187	31.1	199	27.7
≥30	116	19.3	114	15.9
<i>Menopausal status</i>				
Yes	513	85.4	556	77.6
No	88	14.6	161	22.4

Table 2. Prior medical conditions and risk of NHL among Connecticut women

Medical conditions	Cases	Controls	OR <sup>a</sup> (95% CI)
Autoimmune disorders	43	23	2.2 (1.3–3.7)
Anemia	119	121	1.3 (1.0–1.7)
Infectious mononucleosis	36	38	1.2 (0.7–2.0)
Bronchitis	195	229	1.0 (0.8–1.3)
Tuberculosis	10	14	0.9 (0.4–1.9)
Urinary tract infection	224	299	0.8 (0.7–1.0)
Eczema	60	62	1.3 (0.9–1.9)
Psoriasis	22	24	1.1 (0.6–2.0)
Carbuncles	12	5	2.6 (0.9–7.5)
Shingles	36	53	0.8 (0.5–1.2)
Gout	16	27	0.6 (0.3–1.1)
Various disc diseases	33	24	1.6 (0.9–2.8)
Hay fever	96	112	1.0 (0.8–1.4)
Rheumatic fever	11	21	0.6 (0.3–1.2)
Scarlet fever	43	82	0.6 (0.4–0.8)
Asthma	57	66	1.0 (0.7–1.4)

<sup>a</sup> Adjusted for age, BMI, menopausal status, and family history of NHL in first degree relatives.

experienced a 30% increased risk compared to women without anemia (OR: 1.3, 95% CI: 1.0, 1.7). Women with scarlet fever had a 40% significantly reduced risk of NHL (OR: 0.6, 95% CI: 0.4, 0.8).

Table 3 presents the results for selected prior medical conditions associated with NHL subtypes (selected based on overall ten or more exposed cases and controls, and at least one 95% confidence interval excluding null value 1.0). Autoimmune disorders were associated with an increased risk of B-cell NHL (OR: 2.1, 95% CI: 1.2, 3.7), other immunologic NHL (OR: 3.6, 95% CI: 1.6, 8.2), follicular lymphoma (OR: 3.1, 95% CI: 1.5, 6.5), and

diffuse large B-cell lymphoma (OR: 2.1, 95% CI: 1.0, 4.3). Eczema and psoriasis were associated with an increased risk of T-cell NHL (OR: 2.5, 95% CI: 1.1, 5.7; OR: 3.7, 95% CI: 1.3, 10.6, respectively). Various disc diseases showed an increased risk of T-cell NHL (OR: 3.1, 95% CI: 1.1, 9.0) and marginal zone B-cell lymphoma (OR: 3.0, 95% CI: 1.0, 9.5). On the other hand, scarlet fever was associated with a reduced risk of B-cell NHL (OR: 0.5, 95% CI: 0.3, 0.8) and B-cell chronic lymphocytic leukemia (OR: 0.3, 95% CI: 0.1, 1.0).

Table 4 presents the results for medication use and risk of NHL. The longest use of steroidal anti-inflam-

Table 3. Selected medical conditions and risk of NHL subtypes among Connecticut women<sup>a</sup>

NHL subtype	Autoimmune disorders		Various disc diseases		Eczema		Psoriasis		Scarlet fever	
	Ca/Co <sup>b</sup>	OR <sup>c</sup> (95% CI)	Ca/Co <sup>b</sup>	OR <sup>c</sup> (95% CI)	Ca/Co <sup>b</sup>	OR <sup>c</sup> (95% CI)	Ca/Co <sup>b</sup>	OR <sup>c</sup> (95% CI)	Ca/Co <sup>b</sup>	OR <sup>c</sup> (95% CI)
<i>Immunologic cell type</i>										
B-cell	33/23	2.1(1.2–3.7)	25/24	1.6(0.9–2.8)	40/62	1.1(0.7–1.6)	13/24	0.8(0.4–1.6)	32/82	0.5(0.3–0.8)
T-cell	1/23	0.6(0.1–4.4)	5/24	3.1(1.1–9.0)	8/62	2.5(1.1–5.7)	5/24	3.7(1.3–10.6)	6/82	1.3(0.5–3.2)
Other	9/23	3.6(1.6–8.2)	3/24	1.0(0.3–3.6)	12/62	2.0(1.0–3.9)	4/24	1.5(0.5–4.5)	5/82	0.5(0.2–1.2)
<i>REAL<sup>d</sup>classification</i>										
B-CLL	3/23	1.4(0.4–4.9)	3/24	1.5(0.4–5.3)	5/62	1.0(0.4–2.6)	1/24	0.4(0.1–3.4)	3/82	0.3(0.1–1.0)
FL	13/23	3.1(1.5–6.5)	9/24	2.0(0.9–4.4)	10/62	0.9(0.4–1.7)	3/24	0.6(0.2–2.1)	11/82	0.7(0.4–1.3)
MZBL	1/23	0.6(0.1–5.0)	4/24	3.0(1.0–9.5)	3/62	1.1(0.3–3.9)	2/24	1.6(0.4–7.3)	1/82	0.2(0.0–1.3)
DLBL	14/23	2.1(1.0–4.3)	9/24	1.3(0.6–3.0)	19/62	1.3(0.7–2.3)	4/24	0.6(0.2–1.9)	14/82	0.6(0.4–1.2)

<sup>a</sup> Selected based on overall 10 or more exposed both cases and controls, and at least one 95% confidence interval of NHL subtypes excluding null value 1.0.

<sup>b</sup> Number of cases and controls.

<sup>c</sup> Adjusted for age, BMI, menopausal status, and family history of NHL in first degree relatives.

<sup>d</sup> B-CLL – B-cell chronic lymphocytic leukemia; FL – Follicular lymphoma; MZBL – Marginal zone B-cell lymphoma; DLBL – Diffuse large B-cell lymphoma.

Table 4. Prior medication use and risk of NHL by duration of use among Connecticut women

Medicine	Duration <sup>a</sup>							
	All		Short		Moderate		Long	
	Ca/Co <sup>b</sup>	OR <sup>c</sup> (95% CI)	Ca/Co <sup>b</sup>	OR <sup>c</sup> (95% CI)	Ca/Co <sup>b</sup>	OR <sup>c</sup> (95% CI)	Ca/Co <sup>b</sup>	OR <sup>c</sup> (95% CI)
Immunosuppressant	4/1	5.9 (0.6–53.5)	1/1	1.4(0.1–23.9)	3/0	–		
Anti-acne	8/6	2.2 (0.7–6.5)	1/2	1.0(0.1–11.0)	2/2	1.6(0.2–11.5)	5/2	3.9(0.7–20.8)
Anti-inflammatory drugs (steroid)	25/19	1.5 (0.8–2.9)	3/4	0.9(0.2–4.1)	4/7	0.7(0.2–2.5)	18/8	2.6(1.1–6.1)
Anti-inflammatory drugs (non-steroid excluding aspirin)	38/38	1.0(0.6–1.7)	11/13	0.9(0.4–2.0)	18/13	1.4(0.7–3.0)	9/12	0.8(0.3–1.9)
Aspirin	29/45	0.7(0.4–1.2)	6/15	0.5(0.2–1.2)	4/15	0.3(0.1–0.9)	19/15	1.4(0.7–2.9)
Tranquilizers	28/27	1.3(0.8–2.3)	3/10	0.4(0.1–1.4)	9/9	1.4(0.5–3.5)	16/8	2.4(1.0–5.6)
Anti-convulsant drugs	11/10	1.3(0.6–3.2)	3/3	1.2(0.2–6.1)	4/3	1.7(0.4–7.5)	4/4	1.1(0.3–4.7)
Oral contraceptives	129/160	1.1(0.8–1.5)	51/53	1.3(0.8–2.1)	46/55	1.1(0.7–1.8)	32/52	0.8(0.5–1.3)
Estrogen replacement therapy	123/166	0.7(0.6–1.0)	40/52	0.7(0.5–1.1)	44/49	0.9(0.6–1.3)	38/65	0.6(0.4–0.9)
Pain relievers (excluding aspirin)	17/19	1.0(0.5–2.0)	5/8	0.7(0.2–2.1)	3/5	0.7(0.2–3.2)	9/6	1.7(0.6–4.9)
Bronchodilators	17/19	1.0(0.5–2.0)	4/7	0.6(0.2–2.1)	8/7	1.3(0.5–3.6)	5/5	1.2(0.3–4.1)
Antidepressants	39/53	0.8(0.5–1.3)	18/18	1.1(0.6–2.1)	13/19	0.8(0.4–1.8)	8/16	0.6(0.2–1.4)
Thyroid hormones	68/86	0.9(0.6–1.2)	30/29	1.2(0.7–2.0)	20/34	0.6(0.3–1.1)	16/23	0.8(0.4–1.5)
Anti-histamines	16/20	0.9(0.5–1.8)	3/6	0.6(0.1–2.3)	6/8	0.8(0.3–2.4)	7/6	1.5(0.5–4.7)
Digitalis	15/24	0.7(0.4–1.4)	5/6	0.9(0.3–3.1)	4/10	0.5(0.2–1.6)	6/8	0.8(0.3–2.3)
HMG-CoA reductase inhibitors	37/71	0.5(0.4–0.8)	10/28	0.4(0.2–0.8)	8/25	0.3(0.1–0.8)	19/18	1.2(0.6–2.3)
β-Adrenergic blocking agents	31/66	0.5(0.3–0.8)	6/19	0.3(0.1–0.8)	13/27	0.5(0.3–1.0)	12/19	0.7(0.3–1.5)
Non-insulin dependent diabetic medications	22/40	0.5(0.3–0.9)	4/12	0.3(0.1–1.0)	8/15	0.4(0.2–1.1)	10/13	0.8(0.3–1.7)

<sup>a</sup> Categorizing duration into tertile based on the distribution of controls' duration of use.  
<sup>b</sup> Number of cases and controls.  
<sup>c</sup> Adjusted for age, BMI, menopausal status, and family history of NHL in first degree relatives.

matory drugs was associated with an increased risk of NHL (OR: 2.6, 95% CI: 1.1, 6.1). Use of non-steroidal anti-inflammatory drugs was not associated with the risk. However, aspirin users with a moderate duration of use experienced 70% reduced risk of NHL (OR: 0.3, 95% CI: 0.1, 0.9), but not for overall users (OR: 0.7, 95% CI: 0.4, 1.2) and longest users (OR: 1.4, 95% CI: 0.7, 2.9). The longest use of tranquilizers was associated with a borderline increased risk of NHL (OR: 2.4, 95% CI: 1.0, 5.6). On the other hand, the longest use of estrogen replacement therapy was associated with a 40% reduced risk (OR: 0.6, 95% CI: 0.4, 0.9). The reduced risk was also observed for overall users, but the result was not statistically significant (OR: 0.7, 95% CI: 0.6, 1.0). A reduced risk was also associated with use of HMG-CoA reductase inhibitors to lower cholesterol, β-adrenergic blocking agents, and medications for non-insulin dependent diabetes, but reached statistically significant, only among those with a short or moderate duration of use.

Table 5 presents the risks of NHL subtypes associated with selected medications. Estrogen replacement therapy

was associated with a reduced risk for other immunologic NHL (OR: 0.5, 95% CI: 0.3, 0.9) and diffuse large B-cell lymphoma (OR: 0.6, 95% CI: 0.4, 0.9). HMG-CoA reductase inhibitors were associated with a reduced risk for B-cell NHL and B-cell chronic lymphocytic leukemia (OR: 0.6, 95% CI: 0.4, 0.9; OR: 0.1, 95% CI: 0.0, 0.8, respectively). Aspirin use was associated with a borderline reduced risk for diffuse large B-cell lymphoma (OR: 0.4, 95% CI: 0.1, 1.0). Both β-adrenergic blocking agents and non-insulin dependent diabetic medications were associated with B-cell NHL (OR: 0.5, 95% CI: 0.3, 0.8; OR: 0.4, 95% CI: 0.2, 0.8, respectively) and diffuse large B-cell lymphoma (OR: 0.4, 95% CI: 0.2, 0.9; OR: 0.4, 95% CI: 0.1, 0.9, respectively).

Use of tranquilizers was associated with an increased risk of follicular lymphoma (OR: 2.4, 95% CI: 1.1, 4.9, data not shown). No significantly increased risks of NHL subtype were observed for steroidal anti-inflammatory drugs. However, increased ORs were observed for B-cell NHL (OR: 1.5, 95% CI: 0.8, 2.8) and B-cell chronic lymphocytic leukemia (OR: 2.6, 95% CI: 0.8, 8.1, data not shown).

Table 5. Selected medications associated with decreased risk of NHL subtypes among Connecticut women<sup>a</sup>

NHL subtype	Estrogen replacement therapy		HMG-CoA reductase inhibitors		Aspirin		Beta-adrenergic blocking agents		Non-insulin dependent diabetic medications	
	Ca/Co <sup>b</sup>	OR <sup>c</sup> (95% CI)	Ca/Co <sup>b</sup>	OR <sup>c</sup> (95% CI)	Ca/Co <sup>b</sup>	OR <sup>c</sup> (95% CI)	Ca/Co <sup>b</sup>	OR <sup>c</sup> (95% CI)	Ca/Co <sup>b</sup>	OR <sup>c</sup> (95% CI)
<i>Immunologic cell type</i>										
B-cell	102/166	0.8(0.6–1.0)	30/71	0.6(0.4–0.9)	21/45	0.7(0.4–1.1)	23/65	0.5(0.3–0.8)	14/40	0.4(0.2–0.8)
T-cell	81/166	0.8(0.3–1.7)	2/71	0.4(0.1–1.7)	2/45	0.7(0.2–3.1)	4/65	0.9(0.3–2.7)	1/40	0.3(0.0–2.2)
Other	13/166	0.5(0.3–0.9)	5/71	0.5(0.2–1.3)	6/45	1.0(0.4–2.5)	4/65	0.5(0.2–1.3)	7/40	1.3(0.5–3.2)
<i>REAL<sup>d</sup> classification</i>										
B-CLL	14/166	1.0(0.5–1.8)	1/71	0.1(0.0–0.8)	2/45	0.4(0.1–1.6)	4/65	0.5(0.2–1.6)	1/40	0.3(0.0–2.0)
FL	30/166	0.8(0.5–1.3)	7/71	0.5(0.2–1.1)	10/45	1.2(0.6–2.5)	7/65	0.5(0.2–1.2)	4/40	0.4(0.1–1.2)
MZBL	7/166	0.5(0.2–1.3)	3/71	0.6(0.2–2.0)	3/45	0.9(0.3–3.3)	3/65	0.7(0.2–2.2)	1/40	0.2(0.0–2.0)
DLBL	37/166	0.6(0.4–0.9)	13/71	0.7(0.4–1.3)	5/45	0.4(0.1–1.0)	8/65	0.4(0.2–0.9)	5/40	0.4(0.1–0.9)

<sup>a</sup> Selected based on overall 10 or more exposed both cases and controls, and at least one 95% confidence interval of NHL subtypes excluding null value 1.0.

<sup>b</sup> Number of cases and controls.

<sup>c</sup> Adjusted for age, BMI, menopausal status, and family history of NHL in first degree relatives.

<sup>d</sup> B-CLL – B-cell chronic lymphocytic leukemia; FL – Follicular lymphoma; MZBL – Marginal zone B-cell lymphoma; DLBL – Diffuse large B-cell lymphoma.

## Discussion

In this population-based case-control study of NHL, an excess risk was associated with a history of autoimmune disorders, such as rheumatoid arthritis, lupus erythematosus, Sjogren's syndrome, and multiple sclerosis. An increased risk was also observed for anemia, various disc disease, eczema, and psoriasis. Use of steroidal anti-inflammatory drugs and tranquilizers also showed an increased risk. A reduced risk of NHL was observed for subjects who had had scarlet fever and who had used several medications, such as estrogen replacement therapy, aspirin, HMG-CoA reductase inhibitors,  $\beta$ -adrenergic blocking agents, and non-insulin dependent diabetic medications. The observed associations appeared to vary based on NHL subtypes.

Our results linking autoimmune disorders to NHL risk are consistent with previous epidemiological studies [3–6, 32–34]. An increased risk of NHL associated with autoimmune disorders has been attributed to the disturbance of immune system function and/or subsequent immunosuppressive therapy among autoimmune disorder patients [4, 5]. Eczema and psoriasis, two chronic skin conditions, were associated with an increased risk of T-cell NHL in this study. Many previous clinical reports have provided strong evidence for a positive association between T-cell lymphoma and eczema [35, 36] consistent with our results. In addition, several epidemiological studies [9–12] also reported an increased risk of NHL associated with eczema. Psoriasis was reported to be associated with an increased risk of NHL

by several previous studies [7, 14–16]. An increased risk of NHL associated with these two skin conditions is biologically plausible since immune deficiencies in eczema or psoriasis patients are widespread [10, 11, 15].

Previous epidemiological studies have reported an increased risk of high and low grade NHL [11] or no association [7] associated with scarlet fever. In this study, we found that scarlet fever, a disease caused by group A streptococcus bacteria, is associated with a reduced risk for B-cell NHL and B-cell chronic lymphocytic leukemia. Additional epidemiological studies are needed to investigate the relationship. Anemia is a common blood disorder with various causes including nutrient deficiencies, blood loss, chronic diseases, medical treatments, etc. The study by Bernstein and Ross [13] reported an increased risk of NHL associated with anemia. In addition, clinical studies [37, 38] have also linked autoimmune hemolytic anemia and aplastic anemia to NHL. Although the underlying mechanism linking anemia to NHL is unclear, it could be due to the underlying medical cause of anemia, or the subsequent medical treatments associated with the disease.

Estrogen replacement therapy has been inconsistently linked to NHL risk. An early result (seven year follow-up) from the Iowa Women's study reported [20] no association between estrogen replacement therapy and NHL risk. Five years later (13 years follow-up), the authors [19] suggested an increased risk for follicular NHL but not for diffuse NHL or small lymphocyte NHL.

An earlier study by Bernstein and Ross from Los Angeles [13] reported an OR of 1.58 (95% CI: 1.09–

2.29) for women who had reported using estrogen replacement therapy for more than 12 months compared to those who had never used estrogen replacement therapy. In their more recent study [23] that only included women diagnosed with high or intermediate grade NHL, the authors reported a 40% risk reduction for NHL associated with hormone replacement therapy (HRT) (OR: 0.60, 95% CI: 0.31–1.18). The study also found that use of oral contraceptives was related to a reduced risk (OR: 0.47, 95% CI: 0.26–0.85). Use of lactation suppressants (which contain high levels of long-acting estrogens) in this study was also found to be associated with a reduced risk of NHL (OR: 0.45, 95% CI: 0.27–0.75). A recent study from the Netherlands by Beiderbeck *et al.* [39] observed an OR of 0.5 (95% CI: 0.2–1.2) for ever users of estrogen HRT. Our study results also showed a reduced risk of NHL, with a significantly reduced risk observed for the longest duration of use. Several recent studies have also suggested an inverse relationship between pregnancy, parity and NHL risk [40, 41] although the results linking pregnancy or live birth to NHL risk have been inconsistent.

As discussed elsewhere [42], an inverse relationship between NHL risk and HRT, OC use, and pregnancy is biologically plausible [43–50]. Recent studies have shown that estrogen replacement therapy could reduce the secretion of interleukin-6, a potent lymphoid growth and differentiation cytokine [43–47]. Among postmenopausal women, use of HRT has been shown to be inversely associated with body levels of IL-6 [46, 47]. In experimental studies,  $17\beta$ -estradiol has been shown to decrease IL-6 secretion [48, 49]. Thus, increased exposure to estrogens from HRT, OC use or pregnancy would cause a reduction in secretion of IL-6. Studies have shown that higher serum level of interleukin-6 was associated with an increased risk of NHL [50]. Therefore, a reduced secretion of interleukin-6 from increasing estrogen exposure due to HRT, OC use and pregnancy would result in a reduced risk of NHL.

One of our major findings of the study is that long-term use of steroidal anti-inflammatory drugs was associated with an increased risk of NHL, whereas non-steroidal anti-inflammatory drug (excluding aspirin) use was not. The observed relationship is biologically plausible since steroidal anti-inflammatory drugs are immunosuppressive agents while non-steroid anti-inflammatory drugs are not. The small number of exposed cases and controls, however, limited our statistical power to investigate the relationship by NHL subtypes. Several earlier studies also showed a relationship between anti-inflammatory drugs and risk of NHL. A study from Los Angeles by Bernstein and Ross [13]

reported an increased risk of NHL with increasing duration of corticosteroid use and aspirin/other pain reliever use. A study by Doody *et al.* [51] found a weak increased risk of NHL associated with corticosteroids use. A recent study in upstate New York by Kato *et al.* [52] reported that both steroidal and non-steroidal anti-inflammatory drugs are associated with an increased risk of NHL. Another study by Holly *et al.* [53] reported a reduced risk of NHL associated with non-steroidal anti-inflammatory drugs. Aspirin use was associated with a reduced risk of NHL in our study, which is in conflict with an increased risk as reported by Bernstein and Ross [13]. The study by Bernstein and Ross, however, included recent aspirin use in their analyses, which may inflate the association since recent use of aspirin may be a part of the treatment for symptoms caused by NHL. But a recent prospective cohort study among postmenopausal women in Iowa by Cerhan *et al.* [54] reported an increased risk of NHL associated with aspirin and other non-steroidal anti-inflammatory drugs.

A more than twofold increased risk of follicular lymphoma was found among tranquilizer users, mainly among longer-term users. Two earlier case-control studies have also reported an increased risk of NHL associated with use of tranquilizers [11, 13], while another case-control study [29] reported no association between sustained benzodiazepine use and NHL risk.

Several strengths of our study should be considered in interpreting our results. First, the use of incident cases of NHL which were histologically confirmed by experienced study pathologists minimized disease misclassification. Histologic confirmation also allowed for the investigation of the relationship by subtypes of NHL, which is important when studying the etiology of NHL, a heterogeneous group of lymphomas. Second, using a rapid case identification system to identify all eligible NHL cases eliminated survival bias given the aggressive nature of NHL. Third, a relatively large sample size allowed the study to have more power to assess the relationship by various medical history characteristics including the starting age and the duration of medication use, and by NHL subtypes, as well as controlling for potential confounding. And finally, population-based study design reduces the potential for bias due to increased medication use by hospital patients seen in hospital-based studies.

One of the concerns of this study is the self-reported nature of the information on prior medical conditions and medication use rather than reviewing medical records. However, differential misclassification of exposure is unlikely since both the interviewers and the interviewees did not know the study hypothesis related to medical history. Also, unlike breast cancer and other

well-known diseases, little is known about the relationship between past medical history and risk of NHL by the study participants and interviewers. An over-report of past medical conditions by the cases also cannot explain the observed inverse relationships between past medical conditions and medication use and NHL risk found in our study.

Another concern for population-based epidemiological studies is the relative low participation rate from the eligible cases and controls, particularly the older controls. Since so little is known about the relationship between past medical history and medication use and NHL risk, it is unlikely that subject refusal to participate in the study was related to their past specific medical conditions. Also, the fact that our major findings are consistent with previous epidemiological studies lends support to its validity.

While our study included more than 600 female cases and 700 sex-matched controls, the statistical power to investigate the relationship by NHL subtype is still limited, especially for exposures with low frequencies in the study population. Finally, some associations would be expected based on chance alone, given multiple statistical comparisons made by numerous medical conditions and medications used in this study.

In summary, several medical conditions and medication uses have been linked to NHL risk in this population-based case-control study in Connecticut women. An increased risk of NHL observed among women who had a history of autoimmune disorders is consistent with previous observations that primary or acquired immunosuppression, or autoimmune disorders are risk factors for NHL. An increased risk of NHL for women who had used steroidal anti-inflammatory drugs was also consistent with three recent studies and this relationship is biologically plausible since steroidal anti-inflammatory drugs are immunosuppressive agents. The observation that a reduced risk of NHL is associated with HRT is also supported by several recent epidemiological studies linking HRT, oral contraceptive use, and pregnancy to a reduced risk of NHL. Our study results also suggest that the risk related to past medical history and medication use appears to vary by NHL subtypes. Since so little is known about the etiology of NHL, future studies are warranted to further investigate the relationships.

#### Acknowledgements

This study is supported by grant CA62006 from the National Cancer Institute. Certain data used in this study were obtained from the Connecticut Tumor

Registry located in the Connecticut Department of Public Health. The authors assume full responsibility for analyses and interpretation of these data. The authors thank the institutions that allowed access to diagnostic materials and pathology reports, including the following Connecticut hospitals: Charlotte Hungerford Hospital, Danbury Hospital, Greenwich Hospital, Griffin Hospital, Hartford Hospital, Johnson Memorial Hospital, Middlesex Hospital, Lawrence and Memorial Hospital, New Britain General Hospital, Bradley Memorial Hospital, Norwalk Hospital, St. Francis Hospital and Medical Center, St. Mary's Hospital, Hospital of St. Raphael, St. Vincent's Medical Center, Stamford Hospital, William W. Backus Hospital, Waterbury Hospital, Yale-New Haven Hospital, Manchester Memorial Hospital, Rockville General Hospital, Bridgeport Hospital, Windham Hospital, Sharon Hospital, Milford Hospital, New Milford Hospital, Bristol Hospital, MidState Medical Center, and Day-Kimball Hospital.

#### References

1. Zheng T, Mayne ST, Boyle P, *et al.* (1992) Epidemiology of non-Hodgkin's lymphomas in Connecticut, 1935–1988. *Cancer* **70**: 840–849.
2. Hartge P, Devesa SS, Fraumeni Jr JF (1994) Hodgkin's and Non-Hodgkin's Lymphomas. *Cancer Surv* **19/20**: 423–453.
3. Isomaki H, Hakulinen T, Joutsenlahti U (1979) Lymphoma and rheumatoid arthritis. *Lancet* **1**: 392.
4. Gridley G, McLaughlin JK, Ekblom A, *et al.* (1993) Incidence of cancer among patients with rheumatoid arthritis. *J Natl Cancer Inst* **85**: 307–311.
5. Mellemkjaer L, Linet G, Gridley M, Frisch M, Moller H, Olsen JH (1996) Rheumatoid arthritis and cancer risk. *Eur J Cancer* **32A**: 1753–1757.
6. Thomas E, Brewster DH, Black R, Macfarlane GJ (2000) Risk of malignancy among patients with rheumatic conditions. *Int J Cancer* **88**: 497–502.
7. Tavani A, La Vecchia C, Franceschi S, Serraino D, Carbone A (2000) Medical history and risk of Hodgkin's and non-Hodgkin's lymphomas. *Eur J Cancer Prev* **9**: 59–64.
8. Kassan SS, Thomas TL, Moutsopoulos HM, *et al.* (1978) Increased risk of lymphoma in sicca syndrome. *Ann Int Med* **89**: 888–892.
9. Bernard SM, Cartwright RA, Bird CC, Richards G, Lauder I, Roberts BE (1984) Aetiologic factors in lymphoid malignancies: a case-control epidemiological study. *Leuk Res* **8**: 681–689.
10. Cotelingam JD, Witebsky FG, Hsu SM, Blaese RM, Jaffe ES (1985) Malignant lymphoma in patients with the Wiskott–Aldrich syndrome. *Cancer Invest* **3**: 515–522.
11. Cartwright RA, McKinney PA, O'Brien C, *et al.* (1988) Non-Hodgkin's lymphoma: case control epidemiological study in Yorkshire. *Leuk Res* **12**: 81–88.
12. Doody MM, Linet MS, Glass AG, *et al.* (1992) Leukemia, lymphoma, and multiple myeloma following selected medical conditions. *Cancer Causes Control* **3**: 449–456.

13. Bernstein L, Ross RK (1992) Prior medication use and health history as risk factors for non-Hodgkin's lymphoma: preliminary results from a case-control study in Los Angeles county. *Cancer Res* **52**: 5510s-5515s.
14. Arellano F (1997) Risk of cancer with cyclosporine in psoriasis. *Int J Dermatol* **36**(Suppl. 1): 15-17.
15. Hannuksela-Svahn A, Pukkala E, Laara E, Poikolainen K, Karvonen J (2000) Psoriasis, its treatment, and cancer in a cohort of Finnish patients. *J Invest Dermatol* **114**: 587-590.
16. Morales MM, Olsen J, Johansen P, et al. (2003) Viral infection, atopy and mycosis fungoides: a European multicentre case-control study. *Eur J Cancer* **39**: 511-516.
17. Frentz G, Olsen JH (1999) Malignant tumours and psoriasis: a follow-up study. *Br J Dermatol* **140**: 237-242.
18. Boffetta P, Gridley G, Lindelof B (2001) Cancer risk in a population-based cohort of patients hospitalized for psoriasis in Sweden. *J Invest Dermatol* **117**: 1531-1537.
19. Cerhan JR, Vachon CM, Habermann TM, et al. (2002) Hormone replacement therapy and risk of non-Hodgkin lymphoma and chronic lymphocytic leukemia. *Cancer Epidemiol Biomark Prev* **11**: 1466-1471.
20. Cerhan JR, Wallace RB, Folsom AR, et al. (1997) Medical history risk factors for non-Hodgkin's lymphoma in older women. *J Natl Cancer Inst* **89**: 314-318.
21. Vena JE, Bona JR, Byers TE, Middleton E, Swanson MK, Graham S (1985) Allergy-related diseases and cancer: an inverse association. *Am J Epidemiol* **122**: 66-74.
22. McWhorter WP (1988) Allergy and risk of cancer. A prospective study using NHANESI followup data. *Cancer* **62**: 451-455.
23. Nelson RA, Levine AM, Bernstein L (2001) Reproductive factors and risk of intermediate- or high-grade B-cell non-Hodgkin's lymphoma. *J Clin Oncol* **19**: 1381-1387.
24. Anthony JJ (1970) Malignant lymphoma associated with hydantoin drugs. *Arch Neurol* **22**: 450-454.
25. Li FP, Willard DR, Goodman R, Vawter G (1975) Malignant lymphoma after diphenylhydantoin (dilantin) therapy. *Cancer* **36**: 1359-1362.
26. White SJ, McLean AEM, Howland C (1979) Anticonvulsant drugs and cancer. A cohort study in patients with severe epilepsy. *Lancet* **2**: 458-461.
27. Shirts SB, Annegers JF, Hauser WA, Kurland LT (1986) Cancer incidence in a cohort of patients with seizure disorders. *J Natl Cancer Inst* **77**: 83-87.
28. Olsen JH, Boice JD, Jensen JPA, Fraumeni JF (1989) Cancer among epileptic patients exposed to anticonvulsant drugs. *J Natl Cancer Inst* **81**: 803-808.
29. Rosenberg L, Palmer JR, Zauber AG, et al. (1995) Relation of benzodiazepine use to the risk of selected cancers: breast, large bowel, malignant melanoma, lung, endometrium, ovary, non-Hodgkin's lymphoma, testis, Hodgkin's disease, thyroid, and liver. *Am J Epidemiol* **141**: 1153-1160.
30. Herrinton L (1998) Epidemiology of the Revised European-American Lymphoma classification subtypes. *Epidemiol Rev* **20**: 187-203.
31. World Health Organization (1990) *International Classification of Disease for Oncology*, 2nd edn. Geneva, Switzerland: World Health Organization.
32. Kauppi M, Pukkala E, Isomaki H (1997) Elevated incidence of hematologic malignancies in patients with Sjogren's syndrome compared with patients with rheumatoid arthritis (Finland). *Cancer Causes Control* **8**: 201-204.
33. Baecklund E, Ekblom A, Sparen P, Feltelius N, Klareskog L (1998) Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. *BMJ* **317**: 180-181.
34. Rosenthal AK, McLaughlin JK, Gridley G, Nyren O (1995) Incidence of cancer among patients with systemic sclerosis. *Cancer* **76**: 910-914.
35. Amann U, Mielke V, Metze D, Bonsmann G, Schwarz T (1995) Perioral eczema as a manifestation of cutaneous T-cell lymphoma. *Br J Dermatol* **132**: 671-673.
36. Elmer KB, George RM (1999) Cutaneous T-cell lymphoma presenting as benign dermatoses. *Am Fam Physician* **59**: 2809-2813.
37. Sonoki T, Matsuzaki H, Asou N, et al. (1996) Aggressive CD5-positive diffuse large B cell lymphoma showing c-myc rearrangements developed in a patient with autoimmune hemolytic anemia. *Int J Hematol* **63**: 71-76.
38. Jameel T, Anwar M, Abdi SI, Saleem M, Ahmad PA, Khattak MF (1997) Aplastic anemia or aplastic preleukemic syndrome? *Ann Hematol* **75**: 189-193.
39. Beiderbeck AB, Holly EA, Sturkenboom MC, Coebergh JW, Stricker BH, Leufkens HG (2003) No increased risk of non-Hodgkin's lymphoma with steroids, estrogens and psychotropics (Netherlands). *Cancer Causes Control* **14**: 639-644.
40. Cerhan JR, Habermann TM, Vachon CM, et al. (2002) Menstrual and reproductive factors and risk of non-Hodgkin lymphoma: the Iowa women's health study (United States). *Cancer Causes Control* **13**: 131-136.
41. Adami HO, Tsaih S, Lambe M, et al. (1997) Pregnancy and risk of non-Hodgkin's lymphoma: a prospective study [erratum appears in *Int J Cancer* 1997 May 16; **71**(4): 705]. *Int J Cancer* **70**: 155-158.
42. Zheng T, Zhang Y, Morton L, Zhu Y (in press) Re: No increased risk of non-Hodgkin's lymphoma with steroids, estrogens and psychotropics (Netherlands) *Cancer Causes Control*.
43. Jilka RL, Hangoc G, Girasole G, et al. (1992) Increased osteoclast development after estrogen loss: Mediation by interleukin-6. *Science* **257**: 88-91.
44. Cheleuitte D, Mizuno S, Glowacki J (1998) *in vitro* secretion of cytokines by human bone marrow: Effects of age and estrogen status. *J Clin Endocrinol Metab* **83**: 2043-2051.
45. Girasole G, Jilka RL, Passeri G, et al. (1992) 17 beta-estradiol inhibits interleukin-6 production by bone marrow-derived stromal cells and osteoblasts *in vitro*: A potential mechanism for the antiosteoporotic effect of estrogens. *J Clin Invest* **89**: 883-891.
46. Saucedo R, Rico G, Basurto L, Ochoa R, Zarate A (2002) Transdermal estradiol in menopausal women depresses interleukin-6 without affecting other markers of immune response. *Gynecol Obstetric Invest* **53**: 114-117.
47. Rachon D, MySliwska J, Suchecka-Rachon K, Wieckiewicz J, MySliwski A (2002) Effects of oestrogen deprivation on interleukin-6 production by peripheral blood mononuclear cells of postmenopausal women. *J Endocrinol* **172**: 387-395.
48. Rogers A, Eastell R (2001) The effect of 17beta-estradiol on production of cytokines in cultures of peripheral blood. *Bone* **29**: 30-34.
49. Tabibzadeh SS, Santhanam U, Sehgal PB, May LT (1989) Cytokine-induced production of IFN-beta 2/IL-6 by freshly explanted human endometrial stromal cells. Modulation by estradiol-17 beta. *J Immunol* **142**: 3134-3139.
50. Preti HA, Cabanillas F, Talpaz M, Tucker SL, Seymour JF, Kurzrock R (1997) Prognostic value of serum interleukin-6 in diffuse large-cell lymphoma [comment]. *Ann Intern Med* **127**: 186-194.

51. Doody MM, Linet MS, Glass AG, *et al.* (1996) Risks of non-Hodgkin's lymphoma, multiple myeloma, and Leukemia associated with common medications. *Epidemiology* **7**: 131–139.
52. Kato I, Koenig KL, Shore RE, *et al.* (2002) Use of anti-inflammatory and non-narcotic analgesic drugs and risk of non-Hodgkin's lymphoma (NHL) (United States). *Cancer Causes Control* **13**: 965–974.
53. Holly EA, Lele C, Bracci PM, McGrath MS (1999) Case-control study of non-Hodgkin's lymphoma among women and heterosexual men in the San Francisco Bay Area, California. *Am J Epidemiol* **150**: 375–389.
54. Cerhan JR, Anderson KE, Janney CA, Vachon CM, Witzig TE, Habermann TM (2003) Association of aspirin and other non-steroidal anti-inflammatory drug use with incidence of non-Hodgkin lymphoma. *Int J Cancer* **106**: 784–788.