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Vaccination history and risk of non-Hodgkin lymphoma: a population-based, case-control study

Heather A Lankes[1], **Angela J Fought**[1], **Andrew M Evens**[2,3], **Dennis D Weisenburger**[4], and **Brian C-H Chiu**[1,3]

[1]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL

[2]Division of Hematology/Oncology Lymphoma Program, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL

[3]The Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL

[4]Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE

Abstract

Objective—As factors that alter the immune system have been implicated in non-Hodgkin lymphoma (NHL) etiology, it is of interest to explore the association between vaccination and risk of NHL. Results of few epidemiologic studies conducted thus far are inconsistent, and only one has examined the association by histologic subtype.

Subjects—A population-based, case-control study of 387 patients with NHL and 535 controls conducted in Nebraska between 1999 and 2002.

Methods—Information on vaccination for tetanus, polio, influenza, smallpox, and tuberculosis, as well as important environmental factors, was collected by telephone interview. Risk was estimated by odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for confounders.

Results—We found that NHL risk was inversely associated with ever receiving a polio (OR=0.59, CI=0.40–0.87) or smallpox (OR=0.71, CI=0.51–0.98) vaccination, and positively associated with influenza vaccination (OR=1.53, CI=1.14–2.06). No significant association was found for tetanus or tuberculosis vaccination. The patterns of association were similar between men and women. Analysis by histologic subtypes showed that polio vaccination was associated with a lower risk of follicular (OR=0.54, CI=0.31–0.92) and chronic lymphocytic leukemia/small lymphocytic lymphomas (OR=0.29, CI=0.12–0.69) and smallpox vaccination was associated with a lower risk of marginal zone lymphoma (OR=0.41, CI=0.19–0.88). In contrast, ever receiving an influenza vaccination was associated with a higher risk of follicular (OR=1.98, CI=1.23–3.18) and diffuse large B cell lymphomas (OR=1.88, CI=1.13–3.12).

Conclusion—Risk of NHL is inversely associated with polio and smallpox vaccination and positively associated with influenza vaccination. These associations appear to differ by histologic subtype.

Correspondence to: Brian C.-H. Chiu, PhD, Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, 680 North Lake Shore Drive, Suite 1102, Chicago, IL 60611-4402, Phone: 312-503-4672, Fax: 312-908-9588, bchiu@northwestern.edu.

Specific contributions of all authors to published work:
HAL provided input into the statistical analyses and drafted and revised this report. BCC designed and oversaw conduct of the epidemiologic case-control study and provided input into the statistical analyses. DDW was responsible for reviewing cases. HAL, AJF, AME, BCC, and DDW provided input into the data analyses and interpretation. All authors contributed to the final version of this report.

Keywords

non-Hodgkin lymphoma; vaccination; risk factors; epidemiology

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is a malignancy of lymphocytes and factors that alter the immune system appear to play an important role in its development [1]. For example, 25% of individuals with inherited immunodeficiencies will develop NHL during their lifetime [2] and individuals with Acquired Immune Deficiency Syndrome (AIDS) have a >100 times higher risk of developing NHL compared to those without AIDS [3, 4]. Chronic antigenic stimulation has also been proposed as a risk factor for NHL [5] because an increased risk of NHL is found in patients with autoimmune disorders [6, 7] and chronic infections [8–11].

Since autoimmune disorders and chronic infections have been associated with a higher risk of NHL, it is plausible that other mechanisms that induce immune responses, such as vaccination, may also be associated with NHL risk. Only a few studies have evaluated the association between vaccination and NHL risk and the results have been inconsistent. One population-based, case-control study [12] reported that women who received an injected polio vaccine had a significantly lower risk of NHL. Another population-based, case-control study [13] reported a lower risk of small lymphocytic lymphoma in men and women with a history of polio vaccination. In this study, a history of tuberculosis vaccination was associated with a higher risk of small lymphocytic lymphoma. A hospital-based, case-control study by [14] found that a history of polio and tuberculosis vaccination was associated with an increased risk of NHL, whereas a history of smallpox or tetanus vaccination was associated with a lower risk of NHL. In addition, while there is growing evidence suggesting that associations between risk factors and NHL subtype are stronger than associations between the same risk factors and NHL risk in aggregate [15], few studies have evaluated the association of vaccination and NHL risk by subtype [13].

To further evaluate the association between vaccination history and NHL risk, we analyzed data from a population-based, case-control study conducted in Nebraska between 1999 and 2002. We also explored whether these associations differ by NHL subtype.

METHODS

Study Population

A population-based, case-control study was conducted in Nebraska between January 1999 and December 2002. The study population and methods have been reported in detail elsewhere [16, 17]. Briefly, the study was approved by the Institutional Review Board of the University of Nebraska Medical Center. Eligible cases were residents of one of the 66 counties in eastern Nebraska, age 20–75 years, who were alive at the time of initial contact, with newly diagnosed and histologically confirmed NHL, and with no history of human immunodeficiency virus (HIV) infection. Patients were identified by the Nebraska Lymphoma Study Group using a rapid case ascertainment system. Once cases were identified, a physician consent letter explaining the study and requesting permission to contact the patient was sent to the personal physician. Approximately 95% of the incident NHL cases were contacted by a study coordinator within two months of diagnosis. Of the 529 live eligible cases, 387 participated in the study (73.2% participation rate).

Controls without a history of HIV infection or cancer (except squamous cell or basal cell carcinomas of the skin) were randomly selected from the same geographical area as the

cases for frequency matching by age and sex. Eligible controls were identified by two-stage, random digit dialing [18]. Of the 697 live, eligible controls, 535 participated in the study (76.8% participation rate).

Data Collection

Data were collected by a telephone interview that included information on demographics, a history of vaccinations, usual adult height and weight, history of cancer among first degree relatives, past medical history, and other important lifestyle factors. Information on history of vaccination for tetanus, polio, influenza, smallpox, and tuberculosis was obtained by asking the question, “Before two years ago (the date of interview), were you ever vaccinated against tetanus?” The question was repeated for polio, influenza, smallpox, and tuberculosis. Subjects who replied positively to the question were then asked about their age at the first vaccination and the number of vaccinations received. Information on the type of vaccine (e.g., oral versus injected polio vaccine) was not collected.

Data Analysis

Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) [19] to measure the association between vaccination and risk of NHL. All vaccination variables were binary (yes, no) and reflected whether or not the participant had ever received a vaccination for tetanus, polio, influenza, smallpox, or tuberculosis. There was little variation in age at first vaccination and total number of vaccinations received for all vaccinations evaluated except influenza vaccination; therefore, we did not evaluate vaccination dose-response and NHL risk estimates for tetanus, polio, smallpox, and tuberculosis. Analyses were also conducted for six histological subtypes of NHL as defined by the World Health Organization (WHO) classification [20]: (1) follicular lymphoma (including follicular lymphoma grades 1–3 and diffuse follicle center lymphoma grades 1/2; ICD-O-3 codes 9690–9691, 9695, 9698); (2) diffuse large B cell lymphoma (all types; ICD-O-3 codes 9675(b), 9678–9680); (3) small lymphocytic lymphoma (including B cell chronic lymphocytic leukemia; ICD-O-3 codes 9670, 9823); (4) marginal zone lymphoma (including splenic marginal zone B cell lymphoma, extranodal marginal zone B cell lymphoma, and nodal marginal zone B cell lymphoma; ICD-O-3 codes 9689, 9699); (5) “other” miscellaneous subtypes of B cell NHL (including mantle cell lymphoma, precursor B lymphoblastic lymphoma, lymphoplasmacytic lymphoma, Burkitt lymphoma, and unclassified B cell lymphoma); and (6) T cell lymphoma (all types). We also evaluated the association between vaccination and NHL risk by grade. Low grade lymphoma included follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and marginal zone lymphoma. High grade lymphoma included diffuse large B cell lymphoma and other aggressive B cell lymphomas.

Age and gender were included in the final models because controls were frequency matched by these variables to cases. Other potential confounders were considered based on prior knowledge of risk factors for NHL, as well as change-in-estimate criteria [21]. The final model included age (continuous), gender (male, female), and marital status (currently married, not currently married). Factors such as tobacco use, education, body mass index, a family history of cancer, and farming status were not included in the final models because they did not change the risk estimate by more than 10%. Multivariate modeling for vaccination and overall NHL risk was also done separately for men and women. For vaccination and risk of NHL by subtype, we present the results from analysis combining men and women only because the numbers in some subgroups were small and because the patterns of association were similar among men and women. Wald chi-square tests were used to statistically evaluate whether the effect of vaccination on risk of NHL varied by

histologic subtype. The reported p values are two-sided. All statistical analysis was done using SAS software, version 9.1 (SAS Institute, Inc.).

RESULTS

Characteristics of NHL cases and controls are shown in Table 1. Cases and controls were similar with respect to age, gender, race, cancer history, and education. In comparison with the controls, cases were more likely to be currently married and have a higher body mass index.

Table 2 shows a lower risk of NHL was associated with ever having received a polio (OR=0.59; CI=0.40–0.87) or smallpox (OR=0.71; CI=0.51–0.98) vaccination. In contrast, a history of influenza vaccination was associated with a higher risk of NHL (OR=1.53; CI=1.14–2.06). There were no trends with frequency of age at the first influenza vaccination (1–29, 30–44, 45–54, 55+ years) or the number of influenza vaccinations received (1–2, 3–6, 7+) (data not shown). Ever having received a tetanus vaccination was weakly associated with a lower risk of NHL. There was no evidence for an association between tuberculosis vaccination and risk of NHL. The patterns of association were similar in men and women. We also conducted analyses adjusting for the effect of polio, smallpox, and influenza vaccination simultaneously. The point estimates changed slightly, but the conclusion and the patterns of association remain (for polio, OR=0.60, CI=0.40–0.91; for smallpox, OR=0.74, CI=0.51–1.05; and for influenza, OR=1.66, CI=1.21–2.26) (data not shown).

Table 3 shows the associations between vaccination and risk of NHL subtype according to the WHO classification. There was an inverse association between ever receiving a polio vaccination and risk of follicular lymphoma (OR=0.54; CI=0.31–0.92) and chronic lymphocytic leukemia/small lymphocytic lymphoma (OR=0.29; CI=0.12–0.69). Ever receiving a tetanus vaccination was associated with a lower risk of chronic lymphocytic leukemia/small lymphocytic lymphoma (OR=0.21; CI=0.06–0.71), and smallpox vaccination was associated with a lower risk of marginal zone lymphoma (OR=0.41; CI=0.19–0.88). In contrast, a history of influenza vaccination was significantly associated with a higher risk of follicular lymphoma (OR=1.98; CI=1.23–3.18) and diffuse large B cell lymphoma (OR=1.88; CI=1.13–3.12). There was a borderline positive association between ever receiving a tuberculosis vaccination and risk of follicular lymphoma. None of the vaccinations were associated with the risk of T cell lymphoma, although the number of cases was small. When the analyses were conducted by grade, we found an inverse association between risk of low grade lymphoma and ever receiving a polio (OR=0.48, CI=0.31–0.77) or smallpox vaccination (OR=0.63, CI=0.42–0.95) (data not shown). In addition, ever receiving an influenza vaccination was associated with an increased risk of both low grade (OR=1.49, CI=1.02–2.18) and high grade lymphoma (OR=1.90, CI=1.15–3.12) (data not shown).

DISCUSSION

We found that risk of NHL was inversely associated with a history of a polio and smallpox vaccination and positively associated with ever receiving an influenza vaccination. These patterns of association were similar between men and women. In the present study, polio vaccination was associated with a lower risk of low grade lymphoma, in particular, follicular lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma. Smallpox vaccination was also associated with a lower risk of low grade lymphoma, in particular, marginal zone lymphoma. In contrast, a history of influenza vaccination was associated with a higher risk of both low and high grade NHL, in particular, follicular lymphoma and diffuse large B cell lymphoma.

We found that ever receiving an influenza vaccine was associated with a higher risk of NHL. This finding is not entirely consistent with those previously reported [12, 13, 22]. No association was reported in two population-based, case-controls studies [12, 22], whereas a third study [13] reported an inverse association between a history of influenza vaccination and risk of diffuse large B cell lymphoma (OR=0.76, CI=0.62–0.93). It is possible that our findings may be due to chance because we found no consistent dose-response with increasing age at the first influenza vaccination or the number of influenza vaccinations received. However, it remains possible that receiving multiple influenza vaccinations that elicit immune responses to similar influenza surface antigens may be mechanistically similar to autoimmune diseases and chronic infections, which have been suggested as risk factors for NHL [6–11].

In the current study, a history of a polio and smallpox vaccination was associated with a lower risk of NHL, particularly low grade lymphoma. In a population-based case-control study, Bernstein and Ross [12] reported that women who had received an injected polio vaccine were at significantly lower risk of NHL (OR=0.64, CI=0.44–0.93) than women who had not received the vaccine. The association was not statistically significant among men. Holly et al. [23] reported an inverse association between polio vaccination before age 10 and risk of NHL among men (OR=0.51; CI=0.34–0.76), but not among women. In contrast, a hospital-based, case-control study reported that polio vaccination was associated with a higher risk of NHL (OR=1.6, CI=1.2–2.3) [14]. Previous reports on the association of smallpox vaccination with risk of NHL were also inconsistent. Similar to our findings, Holly et al. [23] reported a lower risk of NHL associated with a history of smallpox vaccination among women (OR=0.76; CI=0.58–0.99) and men (OR=0.77; CI=0.60–0.98); however, no association was found in the Bernstein and Ross study [12].

It is unclear why polio and smallpox vaccinations (which are typically received early in life) are inversely associated with the risk of NHL, whereas influenza vaccination (which is typically first received early in life and may be received throughout adulthood) is positively associated with NHL risk. Previous reports have suggested that the balance of T helper 1 (Th1) and Th2 cells may be associated with the risk of lymphoma [24, 25]. A number of factors can affect the immune environment and alter the Th1/Th2 balance. With vaccination, the type of immune response is largely directed by the type of type of vaccination (e.g., live attenuated versus killed whole virus) and the type of adjuvant used (e.g., aluminum hydroxide versus aluminum phosphate) [26, 27]. Additionally, because the immune response changes with age, the age of the recipient at the time of vaccination can influence the magnitude of the response elicited [28]. Our findings may be partly explained by the hygiene hypothesis which suggests that exposure to antigens early in life can alter the immune environment that promotes Th1 and Th2 responses [29]. However, since immunologic data on the type and magnitude of cellular and humoral responses elicited by the specific vaccinations was not available in the present study, the relationships between vaccination and the risk of NHL remain unclear.

Strengths of this study include systematic pathology review of the cases and use of WHO classification, high response rates for cases and controls, and inclusion of only newly diagnosed, histologically-confirmed cases of NHL that occurred in a defined period of time, and in a single geographic area. In addition, cases were identified using a rapid reporting system and thus, minimizing survival bias.

A number of limitations should also be noted. Our data on vaccinations were self-reported. Although self-reported vaccination histories are well-correlated with those obtained by medical review [30–32], misclassification remains possible. Given the lack of public awareness of the association between vaccination history and NHL risk, we would expect

the misclassification to be non-differential, which would underestimate the true association between vaccination history and NHL risk. Secondly, we do not have information on the vaccinations that were required for each subject during early childhood or later in life for work safety, foreign travel, or military purposes. Thirdly, subjects may receive multiple vaccinations and the present study is unable to assess the effect of multiple vaccinations on the immune response and consequently, the risk of NHL. Simultaneous adjustment for polio, smallpox, and influenza changed the point estimates slightly, but the patterns of association remain, suggesting that multiple vaccinations may only account for a portion of the observed associations. In addition, the sample size in our study was too small to examine uncommon histologic NHL subtypes. Thus, our findings should be interpreted cautiously. Finally, vaccination information collected in the present study is limited to those vaccinations that have been suggested to be potential risk factors for NHL and not inclusive of all presently available vaccinations.

In summary, we found that NHL risk is inversely associated with polio and smallpox vaccination and positively associated with influenza vaccination, and that these associations appear to differ by histologic subtype. Future studies should include specific analyses of the cellular and humoral immune responses generated by vaccination, as well as memory responses. Such information may provide a better understanding of the magnitude and types of immune responses generated against various antigens to elucidate the potential mechanisms of vaccination and lymphoma development and/or protection.

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Table 1

Characteristics of NHL cases and controls in Nebraska, 1999–2002

	Cases (n = 387), n (%)[1]	Controls (n = 535), n (%)
Age, years (min, med, max)	(22, 61, 76)	(20, 59, 76)
Gender		
Female	173 (45)	254 (47)
Male	214 (55)	281 (53)
Race		
White	370 (96)	512 (96)
Non-white	17 (4)	23 (4)
Currently Married		
No	92 (24)	173 (32)
Yes	294 (76)	362 (68)
Education		
<High school	18 (5)	15 (3)
High school	146 (38)	226 (42)
>High school	219 (57)	294 (55)
Family History of Cancer		
None	173 (46)	260 (49)
Non-hematopoietic cancer	161 (43)	224 (43)
Hematopoietic cancer	43 (11)	41 (8)
Body Mass Index		
Quartile 1 (<24)	85 (22)	133 (25)
Quartile 2 (24–26.5)	86 (23)	129 (24)
Quartile 3 (26.6–30)	91 (24)	139 (26)
Quartile 4 (>30)	120 (31)	134 (25)

[1]Number of cases and controls may not total 387 and 535, respectively, due to missing data.

Table 2

Vaccination and NHL Risk by Gender for 387 Cases and 535 Controls

	Males				Females				Combined	
Vaccination	**Controls**	**Cases**	**OR**	**(95% CI)[1]**	**Controls**	**Cases**	**OR**	**(95% CI)[1]**	**OR**	**(95% CI)[2]**
Polio										
No	35	35	1.00	reference	22	30	1.00	reference	1.00	reference
Yes	225	172	0.76	(0.46, 1.27)	226	137	0.41	(0.22, 0.75)	0.59	(0.40, 0.87)
Smallpox										
No	49	41	1.00	reference	49	46	1.00	reference	1.00	reference
Yes	226	167	0.80	(0.50, 1.29)	200	122	0.61	(0.38, 0.98)	0.71	(0.51, 0.98)
Influenza										
No	98	59	1.00	reference	92	42	1.00	reference	1.00	reference
Yes	183	154	1.36	(0.92, 2.01)	162	130	1.80	(1.14, 2.84)	1.53	(1.14, 2.06)
Tetanus										
No	7	9	1.00	reference	18	19	1.00	reference	1.00	reference
Yes	274	205	0.50	(0.18, 1.39)	236	154	0.66	(0.33, 1.32)	0.60	(0.34, 1.05)
Tuberculosis										
No	210	158	1.00	reference	213	145	1.00	reference	1.00	reference
Yes	36	33	1.27	(0.75, 2.13)	21	18	1.37	(0.69, 2.72)	1.30	(0.86, 1.98)

[1] Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated relative to controls and adjusted for age and marital status

[2] Odds ratios (ORs) and 95% confidence intervals (CIs) and 95% CIs were estimated relative to controls and adjusted for age, marital status, and gender

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Table 3

Vaccination and NHL Risk by Histologic Subtype for 387 Cases and 535 Controls

		FL			DLBCL			CLL/SLL			MZL			Other B Cell			T Cell		
Vaccination	**Controls**	**Cases**	**OR[1]**	**(95% CI)**	**Cases**	**OR**	**(95% CI)**	**Cases**	**OR**	**(95% CI)**	**Cases**	**OR**	**(95% CI)**	**Cases**	**OR**	**(95% CI)**	**Cases**	**OR**	**(95% CI)**
Polio																			
No	57	22	1.00	reference	15	1.00	reference	9	1.00	reference	6	1.00	reference	12	1.00	reference	1	1.00	reference
Yes	451	97	0.54	(0.31, 0.92)	85	0.72	(0.38, 1.33)	18	0.29	(0.12, 0.69)	28	0.56	(0.22, 1.43)	64	0.63	(0.32, 1.26)	17	1.86	(0.24, 14.51)
Smallpox																			
No	98	29	1.00	reference	25	1.00	reference	5	1.00	reference	11	1.00	reference	15	1.00	reference	2	1.00	reference
Yes	426	91	0.69	(0.41, 1.08)	76	0.61	(0.36, 1.02)	23	0.76	(0.26, 2.13)	24	0.41	(0.19, 0.88)	60	0.88	(0.47, 1.64)	15	1.73	(0.38, 7.91)
Influenza																			
No	190	27	1.00	reference	23	1.00	reference	12	1.00	reference	9	1.00	reference	24	1.00	reference	6	1.00	reference
Yes	345	96	1.98	(1.23, 3.18)	80	1.88	(1.13, 3.12)	16	0.47	(0.21, 1.07)	26	1.47	(0.66, 3.26)	53	1.28	(0.76, 2.16)	13	1.36	(0.50, 3.72)
Tetanus																			
No	25	8	1.00	reference	8	1.00	reference	5	1.00	reference	2	1.00	reference	5	1.00	reference	0	1.00	reference
Yes	510	115	0.69	(0.30, 1.59)	95	0.51	(0.22, 1.17)	24	0.21	(0.06, 0.71)	33	0.83	(0.18, 3.77)	73	0.64	(0.23, 1.78)	19	--	--
Tuberculosis																			
No	423	95	1.00	reference	82	1.00	reference	22	1.00	reference	30	1.00	reference	57	1.00	reference	17	1.00	reference
Yes	57	21	1.73	(0.99, 3.05)	11	1.04	(0.51, 2.09)	3	1.28	(0.36, 4.63)	4	1.17	(0.39, 3.52)	11	1.36	(0.67, 2.80)	1	0.39	(0.05, 3.07)

FL, follicular lymphoma; DLBCL, diffuse large B-cell lymphoma; CLL/SLL, B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma; MZL, marginal zone lymphoma

[1]Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated relative to controls and adjusted for age, marital status, and gender