Vaccination History and Risk of Lymphoma and Its Major Subtypes

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ABSTRACT

Background: Vaccinations have been hypothesized to play a role in lymphoma etiology, but there are few studies, mixed results, and limited data on lymphoma subtypes. Herein, we investigate the association of vaccinations with risk of major lymphoma subtypes.

Methods: We studied 2,461 lymphoma cases and 2,253 controls enrolled from 2002 to 2014. Participants self-reported history of vaccinations against hepatitis A, hepatitis B, yellow fever, and influenza. Polytomous logistic regression was used to estimate OR and 95% confidence intervals (CI), adjusting for potential confounders.

Results: After multivariable adjustment, vaccination against influenza was inversely associated with lymphoma (OR = 0.82; 95% CI, 0.66–1.02), which was stronger for last vaccination 1+ years before enrollment (OR = 0.71; 95% CI, 0.56–0.91) and for >5 influenza vaccinations (OR = 0.56; 95% CI, 0.46–0.68). Ever vaccination against hepatitis A (OR = 0.81; 95% CI, 0.66–1.00) but not hepatitis B (OR = 0.97; 95% CI, 0.81–1.18) was associated with lymphoma risk, although more recent vaccinations were inversely associated with lymphoma risk for both hepatitis A (<6 years before enrollment, OR = 0.56; 95% CI, 0.40–0.77) and hepatitis B (<9 years before enrollment, OR = 0.72; 95% CI, 0.55–0.93). Ever vaccination against yellow fever was inversely associated with risk (OR = 0.73; 95% CI, 0.55–0.96), and this did not vary by time since last vaccination. Although there was no overall statistical evidence for heterogeneity of vaccination history by lymphoma subtype, the only statistically significant inverse associations were observed for influenza and yellow fever vaccinations with diffuse large B-cell and follicular lymphoma.

Conclusions: Selected vaccinations were inversely associated with lymphoma risk, with time since last vaccination relevant for some of these vaccines.

Impact: Vaccinations against hepatitis A, hepatitis B, yellow fever, and influenza are unlikely to increase lymphoma risk.

Introduction

Lymphomas, consisting of Hodgkin (HL) and non-Hodgkin (NHL) lymphoma, are a heterogeneous group of malignancies with an estimated 90,390 new cases and 21,680 deaths in the United States in 2021 (1). Although our understanding of the etiology of lymphoma remains incomplete, risk of lymphoma or specific lymphoma subtypes has been consistently linked with immune dysregulation, including immunosuppression (e.g., HIV/AIDs, solid organ transplantation, certain drugs) and immune stimulation (e.g., autoimmune conditions, inflammation, and chronic infections; ref. 2). Although additional risk factors have been suggested, overall, much of the etiology of lymphoma remains unexplained.

Vaccinations are used to greatly reduce the risk of infection and disease by using the body's natural defenses to safely develop immunity. Classically, vaccines are thought to generate specificity and memory by the activation of antigen-induced adaptive immune responses that involve B and T cells. Although side effects of vaccines are usually acute and transient, vaccines can elicit an autoimmune reaction with inflammatory manifestations driven by the vaccine or vaccine-associated adjuvant (3). On the other hand, vaccines appear to be able to induce nonspecific beneficial effects, with the strongest epidemiologic data for vaccination with live-attenuated vaccines such as Bacillus Calmette-Guerin (BCG), measles, and oral polio that all have been associated with decreased overall childhood mortality in excess of preventing their target diseases (4). Suggested immunologic mechanisms (5, 6) include heterologous T-cell immunity (e.g., "molecular mimicry") and functional upregulation of innate immune cells through epigenetic and metabolic reprogramming ("trained immunity") of long-lived differentiated cells (e.g., tissue-resident macrophages) or hematopoietic progenitors, which may have long-term persistence. These effects can impact on host and tumor biology as well, such as the use of BCG vaccination to treat noninvasive bladder cancer (5).

Although vaccinations are of potential interest in the etiology of lymphoma, only a relatively few studies have assessed vaccinations and lymphoma risk, with mainly null or protective associations reported (7–15). However most of these studies were small (<1,000 cases; refs. 7, 11, 12, 14, 15); had limited data for lymphoma subtypes (11–15) or used an outdated classification (9, 10, 13, 14); or had limited ability to address potential confounding factors beyond age and sex (10, 11, 14, 15). To address these limitations, we present data from a large case–control study on the association of history of vaccination against yellow fever, hepatitis A, hepatitis B, and influenza with risk of lymphoma. These vaccinations represent a variety of vaccine types, year of introduction, dosing, duration of immunity, targeted populations, and prior associations with lymphoma (**Table 1**). We also systematically evaluate heterogeneity across the major

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Cancer Epidemiol Biomarkers Prev 2022;31:461–70

doi: 10.1158/1055-9965.EPI-21-0383

Table 1. Characteristics of selected vaccines and their association with lymphoma.

Vaccination	Type of vaccine and dosing	Year of initiation in United States	Duration of immunity	Countries with the virus	Target population(s)	Association with lymphoma	Reference
Yellow fever	Composed of two live, attenuated strains of yellow fever virus 17D-204 and 17DD One dose, with recommended revaccination at intervals of 10 years to boost antibody titer	1938	Appears to be lifelong	Africa and South America	Routine vaccination between 9 and 12 months of age in endemic areas Travelers should have the vaccine 10 days prior to being in an endemic area	Protective in three studies and null in a fourth	(31)
Hepatitis A	Both an inactivated and attenuated vaccine available Two doses given 6–12 months apart	1995 in the United States	Between 15 years to lifetime	Indian subcontinent, Africa, Central America, South America, Asia, and Eastern Europe	Travelers to Indian subcontinent, Africa, Central America, South America, Asia, and Eastern Europe In the United States as of 2007, the vaccine is strongly recommended for all children 12–23 months of age	No studies	(32)
Hepatitis B	Both a plasma-derived vaccine (PDV) and recombinant vaccine (RV) The vaccine contains hepatitis B surface antigen Two or three doses, depending on vaccine	1981, with a recombinant version in 1986	At least 25 years in those who showed an adequate initial response to the primary course of vaccinations	Worldwide	Recommended for all infants at birth, for children up to age 18, and adults at high risk	No association in three studies	(33)
Influenza	Currently two major forms: • A trivalent or quadrivalent intramuscular injection (IIV3, IIV4, or RIV4, that is, TIV or QIV), which contains the inactivated form of the virus • A nasal spray of live attenuated influenza vaccine (LAIV, Q/LAIV) An annual dose is required	Large-scale availability beginning in 1945 New versions of the vaccines are developed twice a year	At least 6 months, but declines over time	Worldwide	All people over the age of 6 months	Protective association in three studies, null in one study, and a risk association in one study	(34)

lymphoma subtypes including diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), follicular lymphoma (FL), marginal zone lymphoma (MZL), mantle cell lymphoma (MCL), and Hodgkin lymphoma (HL), while adjusting for potential confounding factors.

Materials and Methods

Study population

This study was reviewed and approved by the Mayo Clinic Human Subjects Institutional Review Board, and all participants provided written informed consent. We have previously published full details of this study conducted at the Mayo Clinic (16). Briefly, we prospectively offered enrollment to all consecutive cases of pathologically confirmed lymphoma, CLL, and HL, who were within 9 months of initial diagnosis at presentation to Mayo Clinic Rochester; age 18 years and older; a resident of Minnesota, Iowa, or Wisconsin at the time of diagnosis; and had no history of lymphoma, leukemia, or HIV/AIDs. A Mayo Clinic hematopathologist reviewed materials for each case to verify the diagnosis and to classify each case according to the WHO Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Tissues (17, 18). Of the 4,523 eligible cases identified from September 1, 2002 to August 31, 2014, 3,221 (71.2%) participated, 363 (8.0%) refused, 92 (2.0%) were lost to follow-up, and 847 (18.7%) had their eligibility expire (failed to consent within 9 months of diagnosis or despite consenting failed to complete the protocol within 12 months of diagnosis).

Clinic-based controls were enrolled from Mayo Clinic Rochester patients who had prescheduled general medical examinations (i.e., not for a diagnostic examination for a specific, active symptom or disease) in the Department of Medicine. Controls were eligible if they had no history of lymphoma, leukemia, or HIV/AIDs, were age 18 years or older, and a resident of Minnesota, Iowa, or Wisconsin at the time of appointment. We used a computer program to randomly select controls, frequency matched to cases on 5-year age group, sex, and geographic location of residence (8 county groupings based on distance from Rochester, Minnesota, and urban/rural status). Of the 4,363 eligible controls identified from September 1, 2002 to August 31, 2014, 2,489 (57.1%) participated, 1,289 (29.5%) refused, and 585 (13.4%) had their eligibility expire (failed to consent within 9 months of selection or despite consenting failed to complete the protocol within 12 months of selection).

Exposure assessment

Participants completed a self-administered questionnaire that included demographic characteristics (age, sex, residence, and years of education); family history of hematologic malignancies; height and weight 2 years prior to survey [used to calculate body mass index (BMI) as weight in kg divided by height in meters squared]; selected lifestyle factors including adult alcohol use (categorized here as never, former, or current use), smoking history (never, former, or current use), and recreational sun exposure (hours per week); and history of vaccination against hepatitis A, hepatitis B, yellow fever, and influenza. We also collected age at last vaccination and total number of influenza vaccinations, because the latter vaccine is available annually.

Statistical analysis

We used logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association of history of each of the vaccinations (hepatitis A, hepatitis B, yellow fever, and influenza) with risk of lymphoma overall, adjusting for the study design variables of age at enrollment, sex, and geographic location of residence. We evaluated potential confounding by adding education (categories: up to high school graduation, education beyond high school/some college, college graduate/1+ years of graduate or professional school, missing), year of first Mayo registration (potential surrogate for health services utilization at Mayo), and factors previously associated with lymphoma in prior studies (19) and in this study (family history of hematologic malignancies, BMI, alcohol use, smoking history, and recreational sun exposure) to the basic model. Individuals with missing data for a given exposure and/or confounding variable were dropped from that logistic regression model, except for time from first vaccination, where the missing data on time was included as a missing category. Because of lack of *a priori* knowledge, we did not attempt to model vaccine-specific confounders. We used polytomous logistic regression (20) to simultaneously model the comparison between controls and each of the eight lymphoma subtypes (CLL/SLL, FL, DLBCL, MZL, MCL, TCL, HL, and all other). We used a 7 df Wald test to assess heterogeneity across the subtypes, and a $P < 0.05$ was considered statistically significant.

Results

Characteristics of the study population

Table 2 summarizes the study population by case–control status. Most participants were white (∼97%), the median age at diagnosis for lymphoma cases was 64 years (range: 18–93) and 58% were male; the median age at enrollment for controls was 62 years (range: 18–91) and 53% were male. Most participants were from Minnesota, with a higher percentage among controls (79%) compared with cases (69%). Age, sex, and residence were adjusted in all models. Controls also had a modestly higher educational level (45% for college graduate or higher compared with 35% for cases) and controls had a much earlier year of first Mayo registration (1984) compared with cases (2003); we therefore adjusted for these variables in the multivariable models. With respect to putative NHL risk factors, cases had a higher BMI, a family history of hematologic malignancies, were more likely to be current smokers, were less likely to drink alcohol, but had similar recreational sun exposure. The most common subtypes were CLL/SLL (26%), FL (22%), and DLBCL (17%).

Vaccinations and lymphoma risk

A substantial percentage of both cases and controls had missing data for the items on prior vaccination against hepatitis A (41% and 43%, respectively), hepatitis B (37% and 40%, respectively), and yellow fever (38% and 39%, respectively), whereas this was not the case for influenza (6% and 4%, respectively), suggesting that participants did not know the answers for the former three vaccines ("don't know" was not a response option). For each of the hepatitis A, B, and yellow fever vaccination questions, we compared item response (missing vs. not missing) and did not find any meaningful differences in distributions (>5%) or means by case/control status, age, sex, residence, education, year registered at Mayo, or family history of NHL, with the exception of a somewhat greater percentage of males versus females not providing a response for the hepatitis B (61% vs. 52%) or yellow fever (61% vs. 52%) questions.

Among those providing a response, the most common vaccinations among controls were influenza (90%) followed by hepatitis B (42%), hepatitis A (31%), and yellow fever (12%). In basic models adjusted for the design variables, vaccinations against influenza, hepatitis A, hepatitis B, and yellow fever were inversely associated with lymphoma risk (**Table 3**). Further adjustment for additional

Table 2. Participant characteristics, Mayo Clinic Case–Control Study of NHL.

Characteristic		Cases ($N = 2,461$) *N* (%)	Controls ($N = 2,253$) *N* (%)
Age (years)			
	Mean (SD)	60.4 (14.2)	61.6 (13.2)
Sex			
	Male	1,420 (57.7)	1,190 (52.8)
	Female	1,041 (42.3)	1,063 (47.2)
Ethnicity			
	White	2,379 (96.7)	2,191 (97.2)
	Other	82 (3.3)	62 (2.8)
Residence			
	Minnesota	1,696 (68.9)	1,789 (79.4)
	Iowa	441 (17.9)	268 (11.9)
	Wisconsin	324 (13.2)	196 (8.7)
Education			
	High school or less	584 (27.8)	517 (24.1)
	Some college/vocational	655 (31.2)	608 (28.3)
	College graduate or higher	862 (41.0)	1,020 (47.6)
	Missing	360	108
Year of 1st Mayo registration			
	Median (range)	2003 (1928–2014)	1984 (1924–2013)
BMI 2 years ago			
	Mean (SD)	28.2 (5.5)	27.6 (5.2)
	Missing	88	71
Family history of hematologic malignancy			
	No	2,117 (86.2)	2,057 (91.5)
	Yes	338 (13.8)	191 (8.5)
	Missing	6	5
Smoking history			
	Never	1,320 (55.2)	1,267 (57.7)
	Former	853 (35.6)	789 (36.0)
	Current	221 (9.2)	138 (6.3)
	Missing	67	59
Alcohol history			
	Never	568 (23.6)	446 (20.1)
	Former	535 (22.2)	454 (20.4)
	Current	1,302 (54.2)	1,321 (59.5)
	Missing	56	32
Recreational sun exposure hours/week			
	Median (range)	10.5 (1.5–21.5)	9.8 (1.5–21.5)
	Missing	348	54
Hepatitis A vaccination			
	Never	1,111 (77.2%)	886 (69.3%)
	Ever	329 (22.8%)	393 (30.7%)
	Missing	1,021	974
Hepatitis B vaccination			
	Never	976 (63.4%)	795 (58.4%)
	Ever	564 (36.6%)	567 (41.6%)
	Missing	921	891
Yellow fever vaccination			
	Never	1,385 (90.6%)	1,211 (88.4%)
	Ever	144 (9.4%)	159 (11.6%)
	Missing	932	883
Influenza vaccination			
	Never	345 (14.9%)	215 (9.9%)
	Ever	1,977 (85.1%)	1,948 (90.1%)
	Missing	139	90
NHL subtype			
	CLL/SLL	644 (26.1)	
	FL	528 (21.5)	
	DLBCL	414 (16.8)	
	MZL	170 (6.9)	
	MCL	127 (5.2)	
	TCL	119 (4.8)	
	HL	181 (7.4)	
	Other	278 (11.3)	

Table 3. Association of vaccinations with lymphoma risk and its major subtypes, Mayo Clinic Case–Control Study, 2002–2014.

Vaccination		Cases *N* (%)	Controls *N* (%)	Basic model[a] OR (95% CI)	Basic model + confounders[b] OR (95% CI)
Hepatitis A	Never	1,111 (77.2%)	886 (69.3%)	1 (reference)	1 (reference)
	Ever	329 (22.8%)	393 (30.7%)	0.65 (0.55–0.78)	0.81 (0.66–1.00)
	Time since last vaccination				
	<6 years	97 (6.7%)	151 (11.8%)	0.49 (0.37–0.64)	0.56 (0.40–0.77)
	6+ years	165 (11.5%)	180 (14.1%)	0.72 (0.57–0.91)	0.92 (0.70–1.20)
	Missing	67 (4.7%)	62 (4.8%)	0.87 (0.60–1.25)	1.18 (0.77–1.81)
Hepatitis B	Never	976 (63.4%)	795 (58.4%)	1 (reference)	1 (reference)
	Ever	564 (36.6%)	567 (41.6%)	0.81 (0.69–0.95)	0.97 (0.81–1.18)
	Time since last vaccination				
	<9 years	190 (12.3%)	226 (16.6%)	0.66 (0.52–0.82)	0.72 (0.55–0.93)
	9+ years	272 (17.7%)	245 (18.0%)	0.91 (0.74–1.12)	1.13 (0.89–1.43)
	Missing	102 (6.6%)	96 (7.0%)	0.89 (0.65–1.20)	1.26 (0.88–1.80)
Yellow fever	Never	1,385 (90.6%)	1,211 (88.4%)	1 (reference)	1 (reference)
	Ever	144 (9.4%)	159 (11.6%)	0.74 (0.58–0.94)	0.73 (0.55–0.96)
	Time since last vaccination				
	<18 years	52 (3.4%)	64 (4.7%)	0.65 (0.44–0.95)	0.68 (0.44–1.04)
	18+ years	64 (4.2%)	69 (5.0%)	0.78 (0.55–1.12)	0.74 (0.50–1.11)
	Missing	28 (1.8%)	26 (1.9%)	0.83 (0.48–1.44)	0.81 (0.42–1.54)
Influenza	Never	345 (14.9%)	215 (9.9%)	1 (reference)	1 (reference)
	Ever	1,977 (85.1%)	1,948 (90.1%)	0.69 (0.57–0.83)	0.82 (0.66–1.02)
	Time since last vaccination				
	<1 year	1,250 (53.8%)	1,112 (51.4%)	0.77 (0.63–0.93)	0.89 (0.71–1.12)
	1+ years	659 (28.4%)	780 (36.1%)	0.57 (0.47–0.70)	0.71 (0.56–0.91)
	Missing	68 (2.9%)	56 (2.6%)	0.80 (0.54–1.20)	0.92 (0.57–1.51)

[a]Adjusted for age, sex, and geographic location of residence [sample size in each model: hepatitis A ($N = 2{,}719$), hepatitis B ($N = 2{,}902$), yellow fever ($N = 2{,}899$), influenza ($N = 4{,}485$)].

[b]Adjusted for age, sex, geographic location of residence, education, year of first Mayo registration, family history of any hematologic malignancies, BMI, alcohol, smoking, and recreational sun exposure [sample size in each model: hepatitis A ($N = 2{,}289$), hepatitis B ($N = 2{,}448$), yellow fever ($N = 2{,}454$), influenza ($N = 3{,}806$)].

demographic (education, year of first Mayo registration) and NHL risk factors (family history of hematologic malignancy, BMI, alcohol use, smoking, and recreational sun exposure) attenuated the inverse associations with hepatitis A (OR = 0.81; 95% CI, 0.66–1.00) and influenza (OR = 0.82; 95% CI, 0.66–1.02), whereas this adjustment eliminated the association with hepatitis B vaccination (OR = 0.97; 95% CI, 0.81–1.18) but did not impact the association with yellow fever vaccination (OR = 0.73; 95% CI, 0.55–0.96). For influenza vaccination, there was also an association with number of vaccinations. Compared to never receiving an influenza vaccination, those with 1 to 5 (OR = 0.81; 95% CI, 0.67–0.98) or >5 (OR = 0.56; 95% CI, 0.46–0.68) vaccinations had a lower risk of lymphoma in the fully adjusted model.

Of the potential confounding factors assessed, the strongest factor was year of first Mayo registration. In analyses stratified on the median year of first Mayo registration, the ORs were consistent between strata in the fully adjusted models for all vaccines except hepatitis A vaccination, where the association in the strata with first registration ≤1984 was attenuated (OR = 0.90; 95% CI, 0.62–1.29) relative to first registration after 1984 (OR = 0.77; 95% CI, 0.61–0.99).

We next investigated time since last vaccination based on the median of time from age at last vaccination to age at diagnosis/enrollment (**Table 3**). In fully adjusted models, only more recent vaccinations against hepatitis A (OR = 0.56; 95% CI, 0.40–0.77) and hepatitis B (OR = 0.72; 95% CI, 0.55–0.93) were associated with risk, whereas there was no important difference in the risk estimates by time since last vaccination against yellow fever. For influenza vaccination, the median split was at <1 year prior to enrollment, and the inverse association was specific to those receiving their first vaccination 1 or more years prior to enrollment (OR = 0.71; 95% CI, 0.56–0.91).

Risk by lymphoma subtype

Figure 1 shows forest plots for the fully adjusted lymphoma subtype-specific associations with each type of vaccination. Although none of the heterogeneity tests for differences by subtypes achieved $P < 0.05$, there were a few notable lymphoma subtype-specific associations. Influenza vaccination was inversely associated with FL (OR = 0.62; 95% CI, 0.45–0.86) and DLBCL (OR = 0.69; 95% CI, 0.47–1.00), with all other ORs near one except for a nonsignificant inverse association with the "other lymphoma" category. A greater number of influenza vaccinations showed a stronger inverse association for both FL (compared with no vaccinations, OR = 0.71 for 1–5 and OR = 0.50 for >5 vaccinations, $P_{trend} < 0.001$) and DLBCL (compared with no vaccinations, OR = 0.82 for 1–5 and OR = 0.60 for >5 vaccinations, $P_{trend} = 0.021$), as shown in **Fig. 2**. Hepatitis A vaccination was not statistically significantly associated with any of the subtypes, although most ORs were less than one with the exception for HL. As with the overall association, hepatitis B vaccination was not associated with any specific lymphoma subtype. Finally, yellow fever vaccination showed a strong inverse association with DLBCL (OR = 0.36; 95% CI, 0.19–0.70), an inverse association with FL (OR = 0.59; 95% CI, 0.35–0.99), and a trend with MZL (OR = 0.49; 95% CI, 0.20–1.17), whereas the other subtypes were all near the null value.

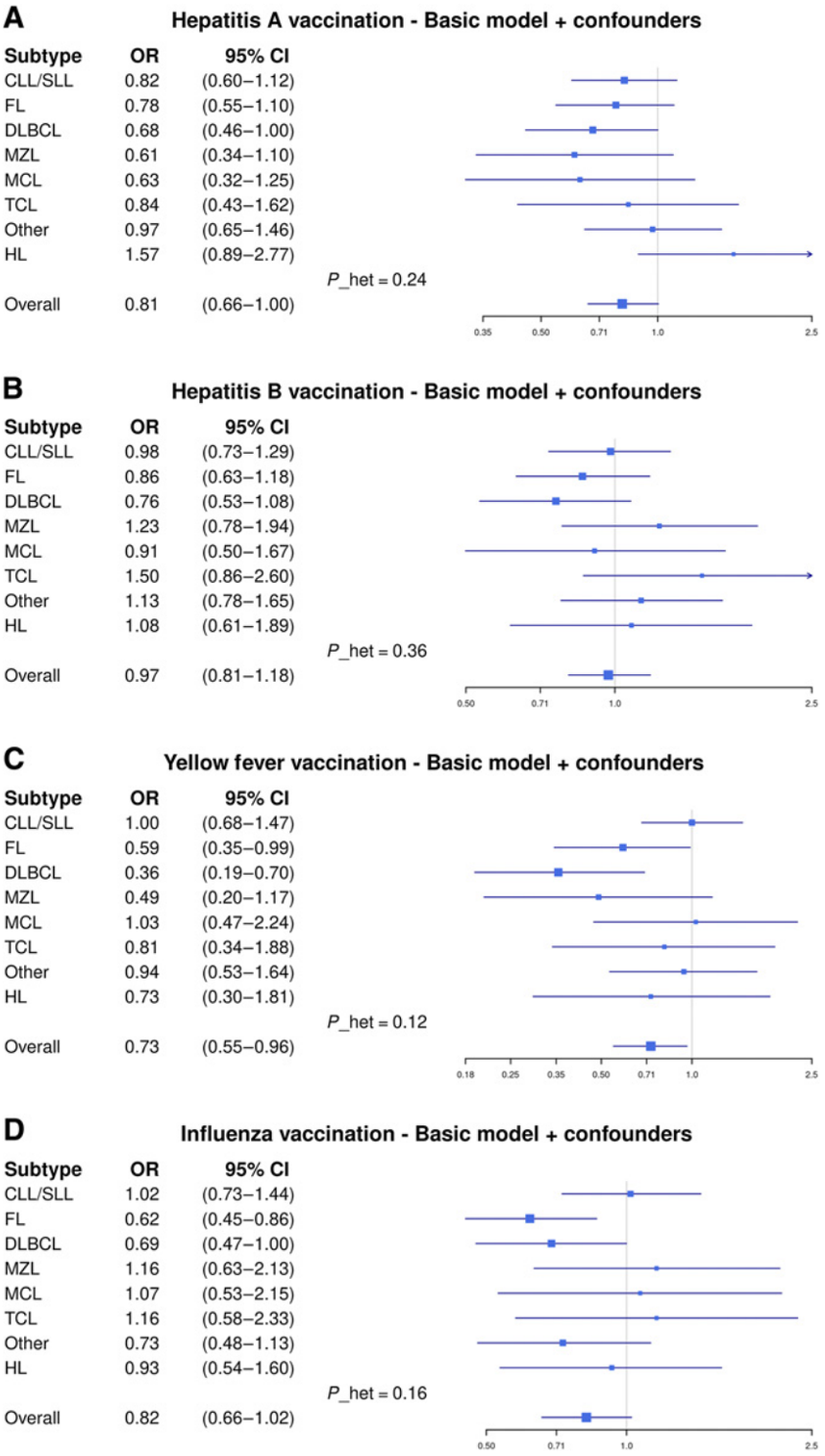

Figure 1.

A–D, Association between vaccinations and lymphoma overall and by subtypes, Mayo Clinic Case-Control Study, 2002–2014. Adjusted for age, sex, geographic location of residence, education, year of first Mayo registration, family history of any hematologic malignancies, BMI, alcohol, smoking, and recreational sun exposure.

Discussion

At over twice the number of cases, this is the largest study to date to investigate the association between history of receiving selected vaccinations with the risk of lymphoma and its major subtypes. After controlling for many possible confounders, we found lymphoma risk was inversely associated with ever receiving influenza, hepatitis A, and yellow fever vaccinations, whereas there was no evidence of an association with hepatitis B vaccination overall, although a vaccination

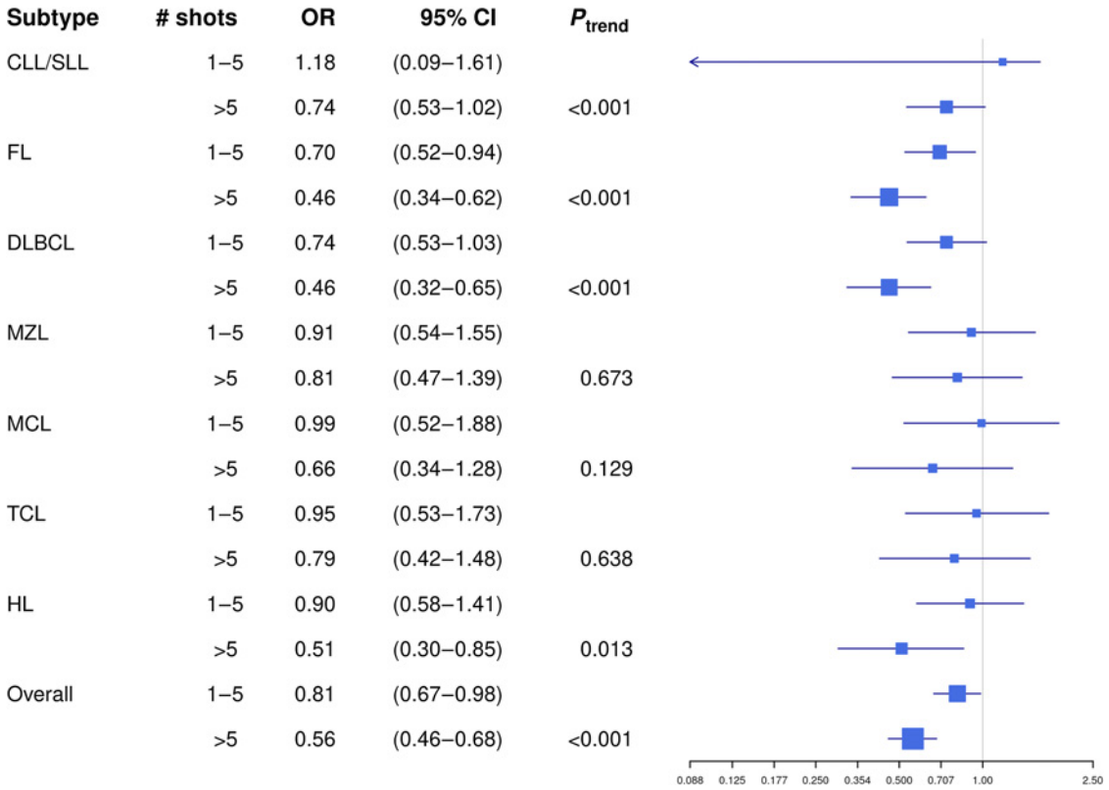

Figure 2.

Association between the total number of influenza vaccinations and lymphoma overall and by their subtypes, Mayo Clinic Case-Control Study, 2002–2014. Adjusted for age, sex, geographic location of residence, education, year of first Mayo registration, family history of any hematologic malignancies, BMI, alcohol, smoking, and recreational sun exposure.

in the past 9 years was inversely associated with risk. Increasing number of influenza vaccinations was also associated with a further lowering of risk. Although none of the heterogeneity tests for lymphoma subtype differences were statistically significant, a majority of subtypes had ORs <1 for hepatitis A vaccinations, whereas only a few lymphoma subtypes had ORs <1 for yellow fever and influenza vaccinations, with statistically significant inverse associations for influenza and yellow fever vaccinations with DLBCL and FL.

Strengths of this study include the large sample size; central pathology review to determine lymphoma subtypes; analysis of major lymphoma subtypes using current classification; assessment of potential confounding by education, family history, BMI, sun exposure, alcohol, and smoking, which were generally not controlled (or not reported) in prior studies but have been previously found to be associated with risk of multiple lymphoma subtypes (19).

There are also limitations. The differential participation rates in cases (71%) and controls (57%) could introduce bias, although as we have previously shown that key drivers of nonparticipation were similar in cases and controls (16), and other aspects of the clinic-based design supported strong internal validity. We had a large number of participants who did not provide responses to the questions on hepatitis A, B, and yellow fever but did provide responses to the influenza vaccination questions, suggesting many did not know the answer for the former three vaccines. Regardless, item nonresponse was not meaningfully correlated with case/control status or other demographic factors. A further limitation was self-report of vaccinations and other exposures, which can lead to misclassification of unknown extent, both differential between cases and controls (introducing bias) and nondifferential misclassification (lowering study power and bias towards the null). Validity of self-reported vaccination status is limited. Most relevant to our study population, a comparison of self-reported vaccination status against electronic health records in community-dwelling patients in a large US health care system reported high sensitivity for influenza vaccination (93.0%), with lower sensitivity for hepatitis A (72.6%) and hepatitis B (62.5%); specificity was highest for hepatitis A (84.0%) and lower but similar for hepatitis B (66.6%) and influenza (65.7%; refs. 21–23). Sensitivity and specificity were higher for report of influenza vaccination in the past year (22, 23). We evaluated a limited number of vaccinations compared with other studies (7, 11–15, 24), which investigated common childhood vaccinations (small pox, polio, BCG, tetanus, diphtheria, measles, rubella) as well as cholera and typhoid. Finally, the study population was almost exclusively white, and thus these results may not generalize to other racial/ethnic groups.

Comparison with prior studies

Our finding of an inverse association with influenza vaccination (OR = 0.82) was somewhat consistent with the largest prior study, a population-based study of 1,281 NHL cases and 2,095 controls who were mostly non-Hispanic white (~80%), conducted in the San Francisco Bay Area of California between 1988 and 1995 (13), which found that influenza vaccination was inversely associated with NHL among women (OR = 0.80; 95% CI, 0.64–1.00) but not among men (OR = 0.92; 95% CI, 0.76–1.10). In a follow-up report evaluating

associations by Working Formulation subtypes (10), inverse associations of influenza vaccination were observed with *ad hoc* defined REAL categories of DLBCL (OR = 0.76; 95% CI, 0.62–0.93) but not FL (OR = 0.92; 95% CI, 0.72–1.20); only DLCBL and FL were statistically significantly associated with influenza vaccination in our study. Further, in a multicenter hospital-based study of 824 lymphoma cases and 752 controls conducted in France between 2000 and 2004 (15), a suggestive inverse association of vaccination against influenza with NHL risk (OR = 0.80; 95% CI, 0.6–1.1) was reported, with decreasing risk with increasing number of influenza vaccinations (OR = 0.6 for >5 vs. no influenza vaccinations, 95% CI, 0.4–1.0) for all NHL, with similar trends for DLBCL and FL, consistent with our findings. Also, consistent with our study, the French study also observed no evidence of an association with HL; however, unlike our study they also observed an inverse association with CLL (15). In contrast, a multicenter, population-based study of 700 lymphoma cases and 700 controls conducted in Germany from 1999 to 2003 (11) found no evidence of an association of influenza vaccination with risk of NHL or HL (11), whereas a population-based study of 387 patients with NHL and 535 controls conducted between 1999 and 2002 in Nebraska (7) found that influenza vaccination was associated with higher risk of NHL (OR = 1.53; 95% CI, 1.14–2.06), and specifically with risk of FL (OR = 1.98; 95% CI, 1.23–3.18) and DLBCL (OR = 1.88; 95% CI, 1.13–3.12; ref. 7). Although all of these studies were conducted in a similar timeframe (1988–2004), it is unclear if the inconsistencies in results relate to the different populations studied, the varying types of vaccines likely used (inactivated vs. live attenuated), the specific strains included in the influenza vaccine over time, or a true lack of any association.

The inverse association with yellow fever vaccination reported here for lymphoma overall (OR = 0.73) is consistent with prior studies of NHL from a population-based study of 619 NHL cases and 619 controls conducted in Los Angeles from 1979 to 1982 (OR = 0.73; 95% CI, 0.53–1.00; ref. 14), the study from San Francisco (OR = 0.70; 95% CI, 0.56–0.88 for men and OR = 0.59; 95% CI, 0.40–0.86 for women; ref. 13), and the study of lymphoma from Germany (OR = 0.8; 95% CI, 0.5–1.3; ref. 11), but not the study of NHL from France (OR = 1.1; 95% CI, 0.8–1.5; ref. 15). The inverse association we observed for DLBCL (OR = 0.36) was also reported in the San Francisco study, albeit that estimate was weaker (OR = 0.67; 95% CI, 0.51–0.89; ref. 10). Of the vaccines we evaluated, yellow fever is one that might be expected to be most affected by confounding by other risk factors because it is only indicated for travel to endemic areas and thus is not widely used in Europe and North America. However, adjustment for a variety of NHL risk factors, including education and lifestyle factors, did not alter the association, although there remains a clear possibility for unknown confounding.

For hepatitis B vaccination, we observed an inverse association with lymphoma risk (including several subtypes) in the basic model, but after adjustment for potential confounding factors the association was null, although more recent vaccination was protective (OR = 0.72). The prior studies from Germany (11) of NHL (OR = 0.96; 95% CI, 0.6–1.5) and from France (15) of NHL (OR = 0.8; 95% CI, 0.6–1.2) found no evidence for associations after basic adjustment for age and sex, while the study from San Francisco (13) reported an inverse association for NHL among men only in age-adjusted analysis (OR = 0.70; 95% CI, 0.51–0.94), but not in multivariable analysis. The San Francisco study did report an inverse association with DLBCL that remained significant after multivariable adjustment (OR = 0.70; 95% CI, 0.50–0.98; ref. 10). Unlike the other vaccines we evaluated, hepatitis B virus (HBV), a small DNA virus, has been linked to cancer in prior studies. In 2009, HBV was judged by IARC to be a Group 1 carcinogen, but to have only limited evidence of a causal link with NHL (25). However, because that report is a meta-analysis of 17 case–control and 5 cohort studies (over 40,000 NHL cases), HBV infection was associated with an increased risk of NHL overall (OR = 2.24; 95% CI, 1.80–2.78; ref. 26), which was restricted to high (OR = 2.73; 95% CI, 1.62–4.59) but not low (OR = 1.11; 95% CI, 0.73–1.69) HBV prevalence countries. A study from Taiwan, where HBV is endemic, reported lower incidence of NHL after the inception of universal HBV vaccination (8). The role of HBV in lymphoma in low HBV prevalence regions such as the United States and Europe requires further evaluation.

Our findings of a protective effect of vaccinations against hepatitis A have not been previously reported, and therefore will require replication.

While intriguing, the current data on the association of vaccination history with risk of lymphoma is mixed. It is notable that most studies show protective or null associations, with relatively few increased risk associations, suggesting that vaccination is unlikely to cause lymphoma. Few data also exist on time from vaccination, and our results suggest variability by vaccine, such that more recent use of hepatitis vaccines were of relevance, whereas yellow fever did not show an effect of time since last vaccination. Our high prevalence of influenza vaccination precluded an informative analysis based on time since vaccination beyond suggesting very recent vaccinations (<1 year) were not protective. Any role of vaccinations in preventing lymphoma requires additional study.

Other vaccines

Prior studies have also investigated the association of other types of vaccinations with lymphoma risk. Although we did not evaluate common childhood vaccines because these have been nearly universally used in the United States for many decades, some older studies and studies outside of the United States have assessed vaccines commonly given in childhood, although only smallpox, polio, BCG, and tetanus vaccinations and risk of lymphoma have been evaluated in more than three studies. Smallpox vaccination, which was discontinued for routine use in the United States in 1972, was protective for NHL in three studies (7, 13) and null in two studies (9, 11), although there was no association for HL (9, 11, 12); of two studies with NHL subtypes data, a protective effect for DLBCL but not for other NHL subtypes was observed (7, 10). Polio vaccination was protective for NHL in women in two studies (7, 13) and in men in one study (13), null in one study (14), and associated with increased risk in one study (12), whereas there was no association for HL (11, 12); limited data on NHL subtype associations found a protective association for CLL/SLL, protective trends for DLBCL, and inconsistent associations for FL (7, 10). BCG vaccination, which is not widely used in the United States, was associated with increased risk of NHL in one study (12) but was null for NHL in 10 other studies (7, 9–11, 14, 15, 27–30). In a meta-analysis of these studies BCG vaccination was associated with increased risk of NHL, however, when restricting to higher quality studies, no association was found (24). BCG vaccination was also null for HL in seven studies (9, 11, 12, 15, 27, 28). In a meta-analysis of these studies BCG vaccination was not associated with HL (24). Follow-up of childhood BCG vaccine trials have found mixed evidence for increased incidence or mortality due to leukemia and lymphoma (which includes both childhood and adult malignancies), with the most recent report after 60 years of follow-up finding no association. Finally, tetanus vaccination was inversely associated with NHL in two studies (11, 12), and suggestive in a third (7), but with mixed results for HL (11, 12); for

NHL subtypes, there were inverse associations with CLL/SLL and DLBCL (7, 10).

Outside of standard childhood vaccinations, cholera vaccination was protective for NHL in two studies (10, 14) and null in two other studies (11, 15), and null for HL in two studies (11, 15); one study reported a protective association for DLBCL (10).

Conclusions

Current studies suggest that vaccination is unlikely to increase risk of lymphoma, and that some vaccinations may be inversely associated with risk. However, any association of vaccination with lymphoma is likely to be specific to a particular vaccine, which is biologically more plausible given the diverse types and immunologic impacts of different vaccines. The current literature is largely based on case–control studies, self-report of vaccination history, limited or no assessment of confounding, and very limited data on lymphoma subtypes. The role of population and sex differences is also under-explored. Future studies should address these limitations. Finally, further biologic studies in companion with epidemiologic data should improve our understanding of any putative role of vaccinations in lymphoma etiology and the associated underlying mechanisms.

Authors' Disclosures

G.S. Nowakowski reports grants from BMS and Roche; grants, personal fees, and non-financial support from Morphosys; and personal fees from TG Therapeutics, Kite, Constellation, Ryvu, Kymera, and Kyropharm outside the submitted work. M.J. Maurer reports grants from National Cancer Institute during the conduct of the study as well as personal fees from Pfizer; grants and personal fees from Morphosys; grants from NanoString, Genentech, and BMS; and personal fees from Kite Pharma outside the submitted work. A.L. Feldman reports other support from Seattle Genetics and Zeno Pharmaceuticals outside the submitted work; in addition, A.L. Feldman has a patent 8,679,743 issued and a patent 9,677,137 issued. N.E. Kay reports grants from CA92153 and CA97274 during the conduct of the study as well as NEK Advisory Board for AbbVie, AstraZeneca, Behring, Cytomx Therapy, Dava Oncology, Janssen, Juno Theraputics, Oncotracker, Pharmacyclics and Targeted Oncology; DSMC (Data Safety Monitoring Committee) for Agios Pharm, AstraZeneca, BMS, Celgene, Cytomx Therapeutics, Janssen, Morpho-sys, and Rigel; and research funding from AbbVie, Acerta Pharma, Bristol Myers Squibb, Celgene, Genentech, MEI Pharma, Pharmacyclics, Sunesis, TG Therapeutics, and Tolero Pharmaceuticals. A.J. Novak reports research funding from Bristol Myers Squibb. T.M. Habermann reports grants from NCI during the conduct of the study as well as other support from Seagen, Tess Therapeutics, Eli Lilly & Co., Morphosys, Incyte, Biegene, and Loxo Oncology outside the submitted work. J.R. Cerhan reports grants from Genentech, NanoString, and BMS; other support from BMS; and non-financial support from Regeneron Genetics Center outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

G. Kleinstern: Conceptualization, formal analysis, visualization, methodology, writing–original draft, writing–review and editing. **M.C. Larson:** Data curation, writing–review and editing. **S.M. Ansell:** Resources, data curation, writing–review and editing. **C.A. Thompson:** Data curation, writing–review and editing. **G.S. Nowakowski:** Data curation, writing–review and editing. **T.G. Call:** Data curation, writing–review and editing. **D.P. Robinson:** Data curation, writing–review and editing. **M.J. Maurer:** Resources, writing–review and editing. **R. Mwangi:** Writing-review and editing. **A.L. Feldman:** Data curation, writing–review and editing. **N.E. Kay:** Data curation, writing–review and editing. **A.J. Novak:** Resources, writing–review and editing. **T.M. Habermann:** Data curation, writing–review and editing. **S.L. Slager:** Methodology, writing–review and editing. **J.R. Cerhan:** Conceptualization, resources, data curation, supervision, funding acquisition, methodology, project administration, writing–review and editing.

Acknowledgments

Research reported in this article was supported by the NCI of the NIH under award number R01 CA92153 and P50 CA97274 (to J.R. Cerhan).

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Received March 25, 2021; revised August 9, 2021; accepted October 29, 2021; published first November 15, 2021.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin 2021;71:7–33.
2. Cerhan JR, Vajdic CM, Spinelli JJ. The non-Hodgkin Lymphomas. In: Thun MJ, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D, editors. Schottenfeld and Fraumeni Cancer epidemiology and prevention. 4th ed. New York: Oxford University Press; 2017. p. 767–96.
3. Guimaraes LE, Baker B, Perricone C, Shoenfeld Y. Vaccines, adjuvants and autoimmunity. Pharmacol Res 2015;100:190–209.
4. de Bree LCJ, Koeken V, Joosten LAB, Aaby P, Benn CS, van Crevel R, et al. Non-specific effects of vaccines: current evidence and potential implications. Semin Immunol 2018;39:35–43.
5. Blok BA, Arts RJ, van Crevel R, Benn CS, Netea MG. Trained innate immunity as underlying mechanism for the long-term, nonspecific effects of vaccines. J Leukoc Biol 2015;98:347–56.
6. Goodridge HS, Ahmed SS, Curtis N, Kollmann TR, Levy O, Netea MG, et al. Harnessing the beneficial heterologous effects of vaccination. Nat Rev Immunol 2016;16:392–400.
7. Lankes HA, Fought AJ, Evens AM, Weisenburger DD, Chiu BC. Vaccination history and risk of non-Hodgkin lymphoma: a population-based, case-control study. Cancer Causes Control 2009;20:517–23.
8. Huang CE, Yang YH, Chen YY, Chang JJ, Chen KJ, Lu CH, et al. The impact of hepatitis B virus infection and vaccination on the development of non-Hodgkin lymphoma. J Viral Hepat 2017;24:885–94.
9. Villumsen M, Sorup S, Jess T, Ravn H, Relander T, Baker JL, et al. Risk of lymphoma and leukaemia after bacille Calmette-Guerin and smallpox vaccination: a Danish case-cohort study. Vaccine 2009;27:6950–8.
10. Holly EA, Bracci PM. Population-based study of non-Hodgkin lymphoma, histology, and medical history among human immunodeficiency virus-negative participants in San Francisco. Am J Epidemiol 2003;158:316–27.
11. Becker N, Deeg E, Nieters A. Population-based study of lymphoma in Germany: rationale, study design and first results. Leuk Res 2004;28:713–24.
12. Tavani A, La Vecchia C, Franceschi S, Serraino D, Carbone A. Medical history and risk of Hodgkin's and non-Hodgkin's lymphomas. Eur J Cancer Prev 2000;9:59–64.
13. Holly EA, Lele C, Bracci PM, McGrath MS. Case-control study of non-Hodgkin's lymphoma among women and heterosexual men in the San Francisco Bay Area, California. Am J Epidemiol 1999;150:375–89.
14. Bernstein L, Ross RK. 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 1992;52:5510s–5s.
15. Monnereau A, Orsi L, Troussard X, Berthou C, Fenaux P, Marit G, et al. History of infections and vaccinations and risk of lymphoid neoplasms: does influenza immunization reduce the risk? Leukemia 2007;21:2075–9.
16. Cerhan JR, Fredericksen ZS, Wang AH, Habermann TM, Kay NE, Macon WR, et al. Design and validity of a clinic-based case-control study on the molecular epidemiology of lymphoma. Int J Mol Epidemiol Genet 2011;2:95–113.
17. Jaffe ES, Harris NL, Stein H, Vardiman JW. World Health Organization Classification of Tumours: pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC Press; 2001.
18. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO Classification of Tumours of the Haematopoietic and Lymphoid Tissues. In: Bosman FT, Jaffe ES, Lakhani SR, Ohgaki H, editors. World Health Organization classification of tumours. Lyon, France: IARC Press; 2008.

19. Morton LM, Slager SL, Cerhan JR, Wang SS, Vajdic CM, Skibola CF, et al. Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr 2014;2014:130–44.
20. Hosmer J, D W, Lemeshow S, Sturdivant RX. Applied logistic regression. New York, NY: John Wiley & Sons; 2013.
21. Rolnick SJ, Parker ED, Nordin JD, Hedblom BD, Wei F, Kerby T, et al. Self-report compared to electronic medical record across eight adult vaccines: do results vary by demographic factors? Vaccine 2013;31:3928–35.
22. King JP, McLean HQ, Belongia EA. Validation of self-reported influenza vaccination in the current and prior season. Influenza Other Respir Viruses 2018;12:808–13.
23. Mac Donald R, Baken L, Nelson A, Nichol KL. Validation of self-report of influenza and pneumococcal vaccination status in elderly outpatients. Am J Prev Med 1999;16:173–7.
24. Salmon C, Conus F, Parent ME, Benedetti A, Rousseau MC. Association between Bacillus Calmette-Guerin (BCG) vaccination and lymphoma risk: a systematic review and meta-analysis. Cancer Epidemiol 2020;65:101696.
25. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, et al. A review of human carcinogens–Part B: biological agents. Lancet Oncol 2009; 10:321–2.
26. Dalia S, Chavez J, Castillo JJ, Sokol L. Hepatitis B infection increases the risk of non-Hodgkin lymphoma: a meta-analysis of observational studies. Leuk Res 2013;37:1107–15.
27. Salmon C, Conus F, Parent ME, Benedetti A, Rousseau MC. Association between Bacillus Calmette-Guerin vaccination and lymphoma: a population-based birth cohort study. J Intern Med 2019;286:583–95.
28. Snider DE, Comstock GW, Martinez I, Caras GJ. Efficacy of BCG vaccination in prevention of cancer: an update. J Natl Cancer Inst 1978;60:785–8.
29. Franceschi S, Serraino D, Bidoli E, Talamini R, Tirelli U, Carbone A, et al. The epidemiology of non-Hodgkin's lymphoma in the north-east of Italy: a hospital-based case-control study. Leuk Res 1989;13:465–72.
30. Kendrick MA, Comstock GW. BCG vaccination and the subsequent development of cancer in humans. J Natl Cancer Inst 1981;66:431–7.
31. World Heath Organization. Vaccines and vaccination against yellow fever. WHO position paper – June 2013. Relev Epidemiol Hebd 2013;88:269–83.
32. World Health Organization. WHO position paper on hepatitis A vaccines – June 2012. Relev Epidemiol Hebd 2012;87:261–76.
33. World Health Organization. Hepatitis B vaccines: WHO position paper – July 2017. Relev Epidemiol Hebd 2017;92:369–92.
34. World Health Organization. Vaccines against influenza WHO position paper – November 2012. Relev Epidemiol Hebd 2012;87:461–76.