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Hepatitis C and Non-Hodgkin Lymphoma Among 4784 Cases and 6269 Controls From the International Lymphoma Epidemiology Consortium

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Abstract

Background & Aims—Increasing evidence points towards a role of hepatitis C virus (HCV) infection in causing malignant lymphomas. We pooled case-control study data to provide robust estimates of the risk of non-Hodgkin's lymphoma (NHL) subtypes after HCV infection.

Methods—The analysis included 7 member studies from the International Lymphoma Epidemiology Consortium (InterLymph) based in Europe, North America, and Australia. Adult cases of NHL (n = 4784) were diagnosed between 1988 and 2004 and controls (n = 6269) were matched by age, sex, and study center. All studies used third-generation enzyme-linked immunosorbent assays to test for antibodies against HCV in serum samples. Participants who were human immunodeficiency virus positive or were organ-transplant recipients were excluded.

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Results—HCV infection was detected in 172 NHL cases (3.60%) and in 169 (2.70%) controls (odds ratio [OR], 1.78; 95% confidence interval [CI], 1.40–2.25). In subtype-specific analyses, HCV prevalence was associated with marginal zone lymphoma (OR, 2.47; 95% CI, 1.44–4.23), diffuse large B-cell lymphoma (OR, 2.24; 95% CI, 1.68–2.99), and lymphoplasmacytic lymphoma (OR, 2.57; 95% CI, 1.14–5.79). Notably, risk estimates were not increased for follicular lymphoma (OR, 1.02; 95% CI, 0.65–1.60).

Conclusions—These results confirm the association between HCV infection and NHL and specific B-NHL subtypes (diffuse large B-cell lymphoma, marginal zone lymphoma, and lymphoplasmacytic lymphoma).

Hepatitis C virus (HCV) infection has been reported to be a prevalent disease since the second half of the 20th century. The infection spread to the general population in some countries such as Japan, Italy, and Egypt, with prevalence estimates ranging from 5% to 10%. In other developed countries the infection largely has been limited to individuals who have received blood transfusions or are intravenous drug users with population prevalence estimates ranging from 1% to 2%.[1, 2 and 3]

A causal role of HCV infection in cirrhosis and hepatocellular carcinoma is well established. Also, HCV has been linked to lymphomagenesis in people with and without type II mixed cryoglobulinemia.[4] However, in the majority of lymphoma studies, small sample sizes have prevented an analysis of the relationship between HCV and single lymphoma subtypes.

Increasing evidence indicates that the association between HCV infection and lymphoma may be owing to viral infection–related chronic antigenic stimulation similar to that reported for *Helicobacter pylori* and gastric mucosa-associated lymphoid tissue lymphoma.[5] The chronic inflammation pathway would be consistent with the association between HCV and several types of lymphomas and with the regression of some lymphomas after eradicating the HCV infection.[6 and 7]

We present results from a large international pooled analysis of the association between non-Hodgkin lymphoma (NHL) and HCV in which HCV infection was determined using a third-generation enzyme-linked immunosorbent assay test to measure HCV antibodies. Our study includes data from 4784 NHL cases and 6269 controls from case-control studies participating in the International Lymphoma Epidemiology Consortium (InterLymph).

MATERIALS AND METHODS

Study Population

InterLymph was established in 2000 as a voluntary consortium to facilitate collaboration among epidemiologic studies of lymphoma (http://epi.grants.cancer.gov/InterLymph).[8 and 9] Through the InterLymph Consortium, 7 case-control studies (3 were multicentric, for a total of 17 participating centers) conducted between 1988 and 2004 were identified as eligible for a pooled analysis. Studies were required to have used the third-generation enzyme-linked immunosorbent assay test for HCV. Detailed information on the association between HCV and NHL risk already has been published for 5[10, 11, 12, 13 and 14] of the 7 studies.

We hereafter refer to each contributing study as they have been published: Connecticut, North–South Italy, National Cancer Institute (NCI)-surveillance epidemiology end result (SEER), New South Wales (NSW), University of California San Francisco (UCSF), EpiLymph (includes 6 countries in Europe), and British Columbia (Table 1). Selected characteristics of each study, including acronym, study site, age range, selection criteria, and participation rates, are presented in Table 1. Of the 17 study centers, 11 used population-based controls and 6 used hospital-based controls. Cases and controls who were human

immunodeficiency virus–positive or organ-transplant recipients were excluded from this analysis. With the exception of the North–South Italy study, all studies frequency-matched their cases and controls by age, sex, and study site. NCI-SEER also frequency-matched cases and controls by race. Local institutional review boards approved all studies and written informed consent was obtained from each participant.

Classification of Non-Hodgkin Lymphoma Subtypes

Four studies, British Columbia, NCI-SEER, NSW, and EpiLymph, used the World Health Organization classification system to define lymphoid neoplasms.[15] The studies conducted in North–South Italy and Connecticut used the Revised European American Lymphoma Classification (REAL) classification system to define NHL subtypes.[16] The UCSF study used both the REAL and the Working Formulation, and cases were recategorized into the World Health Organization classification.

Classification systems from all studies were combined based on the International Classification of Diseases for Oncology[17 and 18] and the World Health Organization classification-based categories developed within the InterLymph Pathology Working Group, with the participation of representative pathologists from each major study.[19] Eleven subtypes were defined for subtypespecific analyses based on morphology and/or immunohistochemistry information: small lymphocytic lymphoma and chronic lymphocytic leukemia, mantle-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, marginal zone lymphoma (MZL), follicular lymphoma (FL), lymphoplasmacytic lymphoma (LPL), other B-cell lymphoma, *Mycosis fungoides* and Sézary syndrome, other T-cell lymphoma, as well as NHL not otherwise specified (NHL NOS).

Statistical Analysis

A preliminary evaluation of categoric exposure variables and the overall NHL risk was conducted using contingency tables analysis and the chi-square test of association.

Heterogeneity in risk estimates between study centers was assessed using the likelihood ratio test under a logistic regression model. The model of interaction between countries and exposure was compared with the model measuring the main effects only for outcomes categorized as dichotomous or polytomous.[20] When the *P* value of the chi-squared statistic was less than .10[21] the risk estimates were considered to be heterogeneous between study centers.

A 2-stage estimation method was followed for risk of overall NHL; such a model allows the control for confounding by individual studies and the consideration of random effects to measure the unexplained interstudy variability.[22] Study-specific risk estimates were calculated using unconditional logistic regression adjusting for sex, age (<35, 35–44, 45–54, 55–64, and ≥65 y), and race (white, black, Asian, and other) because these variables were used for matching in most of the original studies. In addition, any other confounders identified in the preliminary analysis were included in the adjusted models. The study-specific risk estimates obtained after adjustment were weighted by the inverse of the sum of the variance of the individual study estimates to produce a second-stage pooled odds ratio (OR).

For the subtype-specific analysis a joint fixed-effects model was used to allow the inclusion of the studies that found zero HCV prevalence (ie, no cases of HCV infection) for a particular NHL subtype. The risk estimates for specific lymphoma histology subtypes were calculated using polytomous unconditional logistic regression models adjusted for the same variables used in the overall NHL models. The results of lymphoma subtypes that were

found to be associated with HCV infection or those with 10 or more HCV-infected cases are presented graphically, plotting the study summary OR as a black square, whose size is inversely proportional to the variance of the estimate. A horizontal line represents the 95% confidence interval (CI). Diamonds are used to plot the summary OR (estimated using the models described previously) for subtypes. The center of the diamond represents the pooled OR and the extremes show the limits of the 95% CI. A log scale is used for the OR to preserve the symmetry of the CI.

Sensitivity analyses were performed to compare pooled risk estimates after systematically excluding each study to determine whether any single study unduly influenced the pooled estimates. Statistical analyses of the data were conducted using STATA version 9.2 (StataCorp, College Station, TX).

RESULTS

The pooled study included 11,053 participants, 4784 cases and 6269 controls from 7 case-control studies conducted in the United States, Europe, and Australia with information on HCV infection (Table 1). Table 2 describes the prevalence of HCV for cases and controls by sex, age, race, and history of blood transfusion. The pooled study population was predominantly Caucasian (91.79%) and there were differences in the distribution by sex, with a higher proportion of men compared with women (52.26% vs 47.74%). Among controls, HCV was more prevalent among men than among women (3.18% vs 2.15%; $P = .012$), and the prevalence was lower in Asians (0.0%), blacks (1.39%), and whites (2.61%) compared with other ethnic groups (5.01%). Among both cases and controls, HCV was related to transfusion history (ever transfusion vs never: $P < .0001$ and $P = .003$, respectively). The overall prevalence of HCV was stable across age groups in all the studies with the exception of the North–South Italy study that showed an increasing HCV prevalence with increasing age (data not shown).

The pooled HCV prevalence was estimated to be 2.70% (range, 0.39%–10.0%) among controls and 3.59% (range, 0%–30.6%) among cases (Figure 1). The study-specific association between HCV and risk of NHL is presented in Table 3. In the pooled dataset, NHL risk was increased in association with HCV positivity (OR, 1.78; 95% CI, 1.40–2.25). The study-specific associations between HCV and risk of NHL are presented in Table 3; no heterogeneity between the studies was identified ($\chi^2 = 7.44$; df = 6; $P = .28$). History of transfusion was not related independently to lymphoma risk.

There was a wide range of HCV prevalence between the NHL subtypes, with the highest value for Burkitt lymphoma (7.50%) and the lowest value for mantle-cell lymphoma (0.84%) (Table 4). The effect of HCV positivity on risk of NHL varied within the B-cell NHL subtype with the lowest risk noted for mantle-cell lymphoma and the highest for MZL. In particular the risk estimate for DLBCL (OR, 2.24; 95% CI, 1.68–2.99) was statistically different from the one for follicular lymphoma (OR, 1.02; 95% CI, 0.65–1.60). HCV positivity was associated significantly with a statistically significant increase in risk of MZL (OR, 2.47; 95% CI, 1.44–4.23), LPL (OR, 2.57; 95% CI, 1.14–5.79), DLBCL (OR, 2.24; 95% CI, 1.68–2.99), and “other B-cell lymphoma” (OR, 2.36; 95% CI, 1.11–5.01). The “other B-cell lymphoma” category is a mixture of different subentities; the increased risk was restricted to the B NHL NOS group. The risk of Burkitt lymphoma was increased nonsignificantly 2-fold. HCV positivity did not appear to increase the risk of T-cell lymphomas.

Study-specific analyses were performed for those lymphoma subtypes with a statistically significant association with HCV (except the heterogeneous group of “other B-cell

lymphomas") or those with 10 or more cases exposed to HCV (Figure 2). Risk of LPL, chronic lymphocytic leukemia, and FL associated with HCV infection did not differ among studies whereas study differences were observed for DLBCL and MZL. The strongest association between HCV and DLBCL was observed in British Columbia; however, the sensitivity analysis showed no influence of any single study in the overall estimation of risk, although the overall estimate was decreased by the absence of HCV infection among MZL patients in the Connecticut and the NSW study populations. For MZL, a slightly increased risk was observed when the EpiLymph study was excluded (OR, 4.84; 95% CI, 2.30–10.19) and the opposite was observed when the North–South Italy study was excluded (OR, 1.96; 95% CI, 0.94–4.12). In Figure 2, no estimates are available for those lymphoma subtypes with no HCV-positive cases.

DISCUSSION

This pooled analysis to explore the association between HCV infection and risk of NHL subtypes included mostly countries with low background HCV prevalence with the exception of Italy. Our results show increased risks of DLBCL, MZL, and LPL associated with HCV infection. These risk estimates were particularly robust for DLBCL with a 2-fold increased risk overall and a statistically significant increased risk observed in 3 of the 7 studies. Our results are in agreement with several studies mainly from Italy, a high-prevalence country, which also found an association between HCV and DLBCL,[10, 11, 12, 13 and 23] MZL,[24, 25 and 26] and LPL.[27, 28 and 29]

The association observed between HCV and MZL was strongest in the study conducted in North–South Italy, with a 12-fold increased risk. However, sensitivity analyses showed that the overall estimate was decreased by the absence of HCV infection among MZL patients in the Connecticut and the NSW study populations. MZL is a subtype that was not defined formally before the REAL classification[30] and therefore the global incidence of MZL may be underestimated when pooling studies using different classifications. Although the pooled analysis included 385 MZL, with an overall 3-fold increase in risk, a more precise evaluation of this association may require pooling of studies that each used the World Health Organization classification to characterize MZL.

HCV infection was associated with a 3-fold increased risk of LPL. This association was consistent in 4 of 6 studies with LPL cases. LPL includes immunocytoma and Waldenström's disease, both repeatedly identified as related to HCV infection in case-control studies[27, 28 and 29] and in a large cohort of US veterans.[31] LPLs produce an immunoglobulin M paraprotein with autoantibody or cryoglobulin activity. Interestingly, these immunoglobulin Ms also may be present in MZL.[15]

Unlike 3 previous studies[10, 11 and 25] and a recent meta-analysis,[2] our pooled data did not show an increased risk of FL associated with HCV infection, although risk of FL was significantly lower than that of DLBCL. Differences may be owing to the different study inclusion criteria. In the study presented here, we included only case-control studies that used third-generation enzyme-linked immunosorbent assay testing and that provided the individual study records. Other lymphoma subtypes that do not originate from germinal center or postgerminal center B cells, such as mantle-cell lymphoma, Burkitt lymphoma, and T-cell lymphoma, were not related consistently to HCV infection. Our results support the hypothesis that proliferation of specific B-cell clones caused by chronic antigenic stimulation sustained by HCV is a likely mechanism that drives the HCV-mediated pathogenesis of B-cell lymphoma, in particular MZL and DLBCL.

No clear mechanism of direct induction of malignancy by HCV in the lymphocyte population has been shown consistently in vivo. Although earlier work[6] showed lymphoma remission after successful treatment of HCV in patients with splenic lymphoma with villous lymphocytes, there are not yet any follow-up data from well-planned randomized trials to clarify whether antiviral treatment is effective for the remission of lymphoproliferative malignancy in hematologic HCV-positive patients.[32] Such confirmation would imply a benefit from a proven therapeutic tool, and confirm a strong association between HCV and NHL.

Another line of evidence supporting the association between HCV and lymphoma is the consistent association between HCV and mixed cryoglobulinemia. Chronic infection with HCV is strongly associated with mixed cryoglobulinemia type II, which can evolve into overt lymphoma in some patients.[29, 33 and 34] Increasing evidence indicates that MZL of mucosa-associated lymphoid tissue, both nodal and splenic types, are associated with chronic antigenic stimulation by autoantigens and/or bacterial or viral pathogens. These associations could not be tested in this study because no information was collected about history of cryoglobulinemia. Our data warrant further investigation of this issue.

HCV does not integrate into the host genome and it does not contain an obvious oncogene. Little is known about the mechanism of HCV in the activation and alterations of B-cell functions leading to lymphomas. HCV envelope protein E2 interacts with CD81 on the surface of B lymphocytes[35] and with the B-cell receptor of HCV-associated lymphomas.[36] This may jeopardize B-cell function and promote lymphomagenesis. New evidence suggests an important role of HCV infection in the up-regulation of B-lymphocyte stimulator (BLyS).[37] BLyS is expressed by a variety of immune cells and acts on mature B lymphocytes promoting differentiation, proliferation, and survival.[38 and 39] BLyS transgenic mice develop a lupus-like syndrome and finally B-cell lymphoma.[40 and 41] Furthermore, BLyS deregulation has been observed in patients with NHL[42] as well as in several autoimmune diseases that predispose to lymphomas including systemic lupus erythromatosus,[43] Sjögren's syndrome,[44] and rheumatoid arthritis,[45] and in mixed cryoglobulinemia syndrome.[37] Interestingly, BLyS serum levels during chronic HCV infection are correlated significantly with B-cell proliferation.[46] Other contributing factors for which some evidence exists include the following: (1) HCV-mediated induction of a mutator phenotype with a substantial increase in mutation frequency in immunoglobulins and proto-oncogenes,[47 and 48] (2) down-regulation of major histocompatibility complex class II molecules and apoptotic factors,[49] and (3) activation of proinflammatory cytokine production.[50 and 51]

As previously reported,[52] the InterLymph consortium has allowed investigators to pool data from contributing studies, providing adequate statistical power to test hypotheses using fully adjusted models among participants without known immune suppression. These types of initiatives are an excellent alternative when individual studies have low power to test hypotheses related to rare exposures and within small subgroups.

Our results confirm the association between HCV infection and specific B-NHL subtypes (DLBCL, MZL, and LPL). This study had sufficient statistical power to confirm these associations in populations with low HCV prevalence. Our study further emphasizes the need to implement strategic measures to prevent HCV infection and to treat HCV infection adequately.

Abbreviations used in this paper

BLyS	B-lymphocyte stimulator
CI	confidence interval
DLBCL	diffuse large B-cell lymphoma
FL	follicular lymphoma
HCV	hepatitis C virus
InterLymph	International Lymphoma Epidemiology Consortium
LPL	lymphoplasmacytic lymphoma
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NOS	not otherwise specified
NSW	New South Wales
OR	odds ratio
SEER	Surveillance epidemiology end result
UCSF	University of California San Francisco

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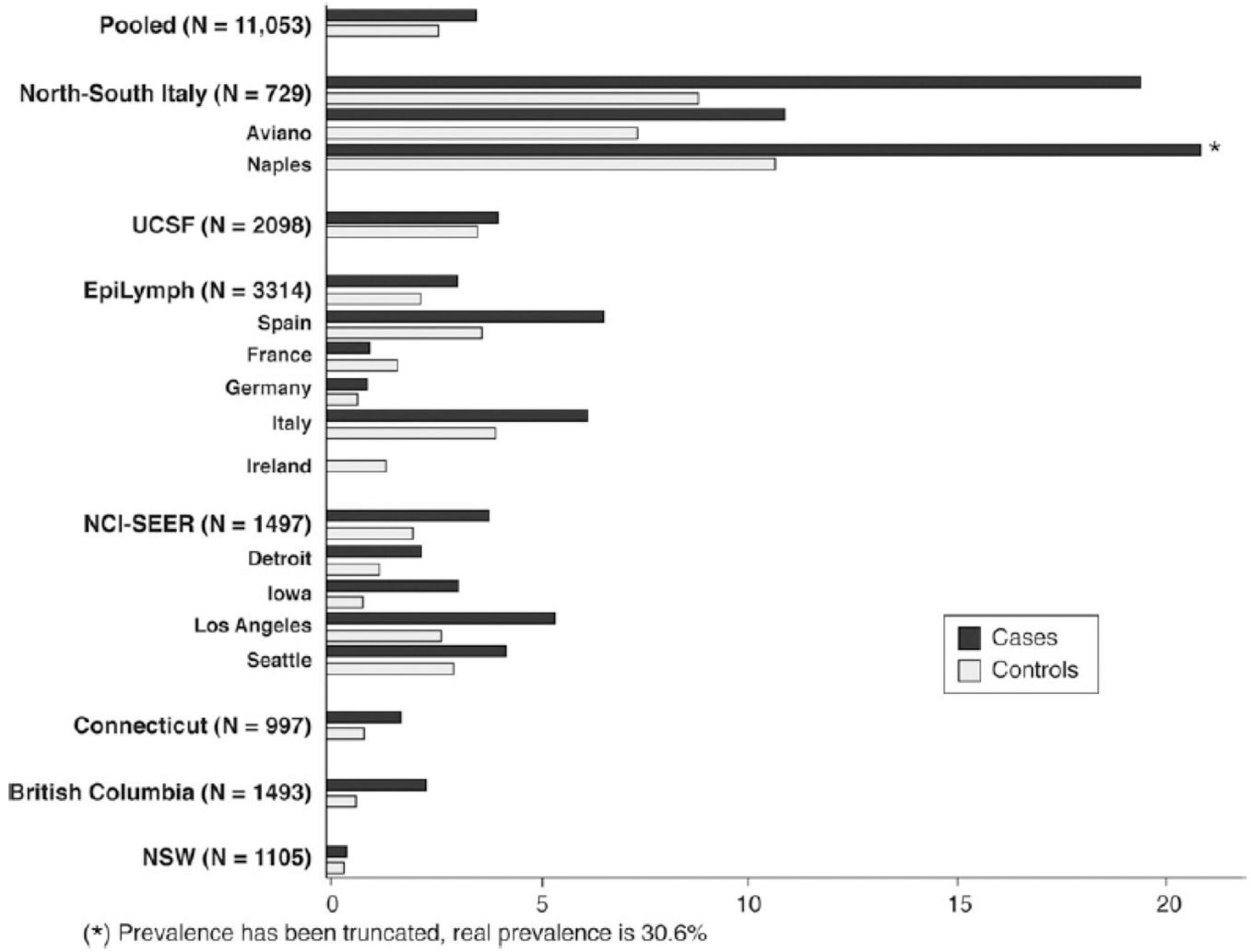

Figure 1.
Prevalence of antibodies against HCV among NHL cases and their respective controls by study.

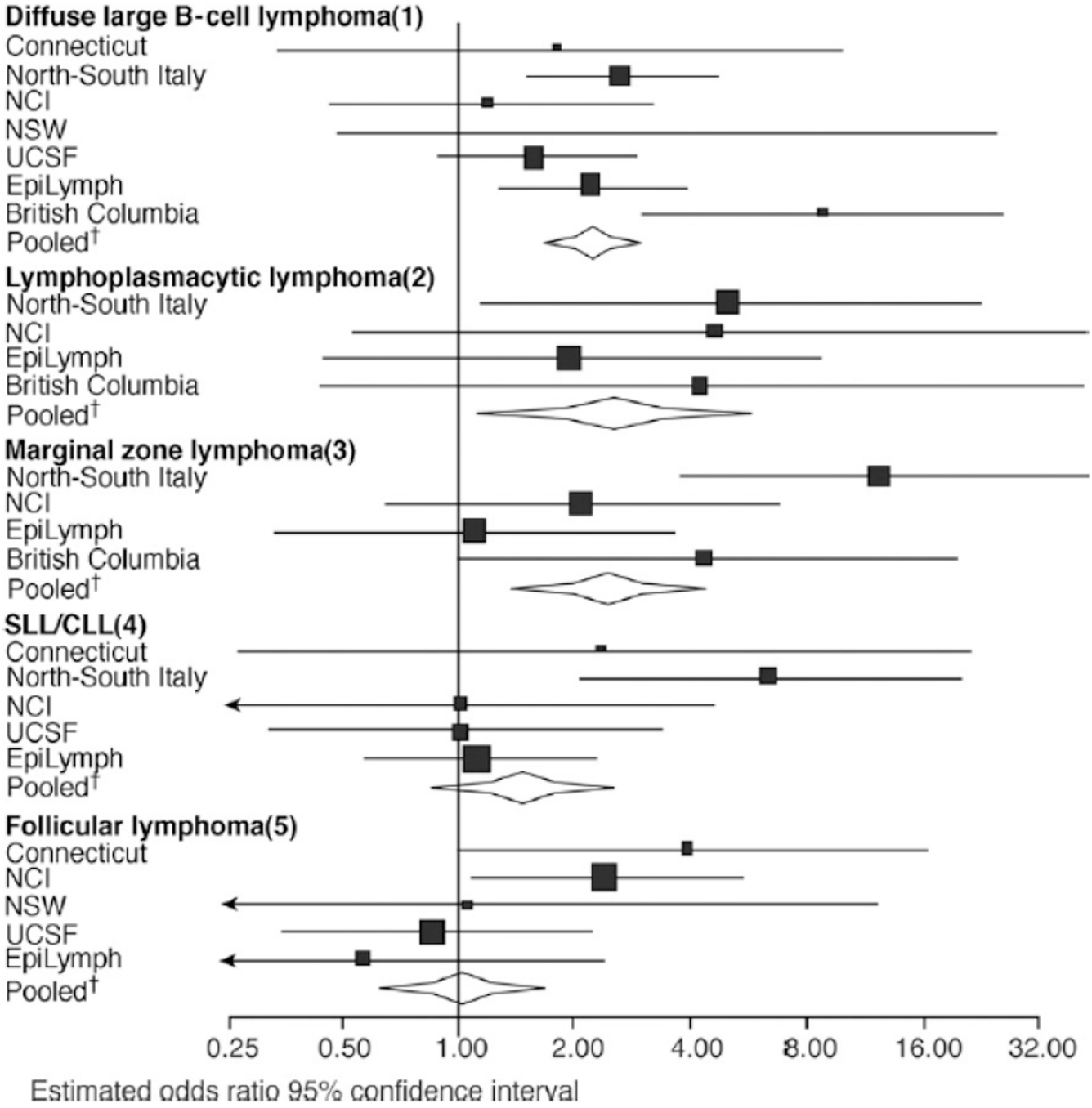

Figure 2.

Risk estimates for lymphoma sub-types associated with HCV by study. SLL/CLL, small-cell lymphocytic lymphoma/chronic lymphocytic leukemia. (1) Heterogeneity test: $\chi^2 = 11.69$; df = 6; $P = .07$. (2) Heterogeneity test: $\chi^2 = 0.90$; df = 3; $P = .83$. (3) Heterogeneity test: $\chi^2 = 8.96$; df = 6; $P = .03$. (4) Heterogeneity test: $\chi^2 = 4.80$; df = 6; $P = .31$. (5) Heterogeneity test: $\chi^2 = 7.79$; df = 4; $P = .10$. †OR and 95% CI obtained from the polytomous unconditional logistic regression using a joint fixed-effects model adjusted for age, sex, race, and study center.

Table 1

Characteristics of Case-Control Studies Included in the Pooled Analysis

			Cases (n = 4784)		
Acronym	**Country: Study center**	**Year**	**Age, y**	**n**	**Participation %**
Connecticut	United States: Connecticut	1995–2001	23–85	463	72
North-South Italy[a]	Italy: Aviano, Naples	1999–2002	18–84	225	>97
NCI-SEER	United States: Detroit, MI; Iowa; Los Angeles, CA; Seattle, WA	1998–2001	20–74	813	76
NSW	Australia: New south Wales; Australian Capital Territory	2000–2002	20–74	587	85
UCSF	United States: San Francisco, CA	1988–1995	21–74	554	72
EpiLymph	Europe: Spain,[a] France,[a] Germany, Italy, Ireland,[a] and Czech Republic[a]	1998–2004	18–89	1346	82–93
British Columbia	Canada: Greater Vancouver Regional District, Capital Regional District	1996–2004	20–82	796	85

Controls (n = 6269)				
Matching criteria	**Source**	**n**	**Participation %**	**Study Reference**
Age	RDD and CMMS	534	RDD, 69; CMMS, 47	11
None	Hospital controls	504	>91	13
Age, sex, and study site	RDD and CMMS	684	52	10
Age, sex, and area of residence	Random selection from electoral rolls	518	61	14
Age, sex, and country of residence	RDD	1544	78	
Age and sex and hospital study site when appropriate	Hospital-based (Spain, France, Ireland, and Czech Republic); population-based controls (Germany and Italy)	1788	44–96	12
Age, sex, and geographic region	Client Registry of the Ministry of Health	697	50	

RDD, random digit dialing; CMMS, Centers for Medicare and Medicaid Services (official abbreviation is CMS).

[a]Hospital-based case-control studies; all other studies were population-based (ie, cases were identified from hospitals and registries).

Table 2

HCV Prevalence by Status and Study Population Characteristics

			HCV prevalence	
	Overall n (%)	**Controls/cases**	**Controls n (%)**	**Cases n (%)**
Included subjects	11,053	6269/4784	169(2.70)	172(3.60)
Sex				
Male	5776 (52.26)	3333/2443	106 (3.18)	97 (3.97)
Female	5277 (47.74)	2936/2341	63 (2.15)	75 (3.2)
P value[a]			.01	.15
Age, y				
<35	860 (7.78)	594/266	11 (1.85)	7 (2.63)
35–44	1280 (11.58)	792/488	23 (2.90)	23 (4.71)
45–54	1959 (17.72)	1073/886	22 (2.05)	39 (4.40)
55–64	2677 (24.22)	1415/1262	43 (3.04)	47 (3.72)
≥65	4277 (38.70)	2395/1882	70 (2.92)	56 (2.98)
P value[a]			.34	.18
Race				
White	10,146 (91.79)	5795/4351	151 (2.61)	157 (3.61)
Asian	126 (1.14)	63/90	0 (0.0)	0 (0.0)
Black	153 (1.38)	72/54	1 (1.39)	3 (5.56)
Others	628 (5.68)	339/289	17 (5.01)	12 (4.15)
P value[a]			.03	.24
History of blood transfusion				
No	9001 (82.10)	5125/3876	123 (2.40)	117 (3.02)
Yes	1899 (17.32)	1067/832	43 (4.03)	51 (6.13)
P value[a]			.003	<0.0001

[a]Chi-squared association *P* value.

Table 3

Risk Estimates (OR, 95% CI) for NHL Associated With HCV by Study

	Prevalence						
	Control	Case	Control		Case		
	n	n	n	%	n	%	OR (95% CI)[a]
Connecticut	534	463	5	0.94	8	1.73	2.80 (0.65–6.64)
Italy	504	225	45	8.93	44	19.56	2.67 (1.66–4.29)
NCI	684	813	14	2.05	32	3.94	1.89 (0.99–3.61)
NSW	518	587	2	0.39	3	0.51	1.15 (0.19–7.00)
UCSF	1544	554	57	3.69	23	4.15	1.24 (0.75–2.05)
EpiLymph	1788	1346	41	2.29	43	3.19	1.44 (0.93–2.24)
British Columbia	697	796	5	0.72	19	2.39	3.28 (1.20–8.98)
Pooled data	6269	4784	169	2.7	172	3.59	1.78 (1.40–2.25)[b]

NOTE. Test of heterogeneity between studies; $P = .28$, $\chi^2 = 7.44$; df = 6.

[a] OR and 95% CI were estimated using unconditional logistic regression models adjusted for age, sex, race, and study center.

[b] Two-stage logistic regression model.

Table 4

Risk (OR and 95% Cls) of NHL Subtypes by HCV Infection

	Total		Prevalence			
	n	%	n	%	OR (95% CI)[a]	*P* value[b]
Lymphoma subtype						
Burkitt	40	0.84	3	7.50	2.42 (0.71–8.27)	.75
Diffuse large B-cell lymphoma	1494	31.24	76	5.09	2.24 (1.68–2.99)	.07
LPL	144	3.01	7	4.86	2.57 (1.14–5.79)	.83
MZL	383	8.00	17	4.44	2.47 (1.44–4.23)	.03
Chronic lymphocytic leukemia/small lymphocytic lymphoma	608	12.71	22	3.62	1.48 (0.92–2.38)	.31
Other B-cell lymphoma[c]	244	5.10	8	3.28	2.36 (1.11–5.01)	.14
Other T-cell lymphoma	206	4.31	6	2.91	1.41 (0.60–3.29)	.71
NHL NOS	248	5.18	7	2.82	1.50 (0.67–3.33)	.90
FL	1181	24.68	23	1.95	1.02 (0.65–1.60)	.10
M fungoides/Sézary syndrome	117	2.45	2	1.71	0.74 (0.18–3.08)	.41
Mantle cell lymphoma	119	2.49	1	0.84	0.60 (0.08–4.41)	NA

NOTE. Subtypes are ordered by HCV prevalence.

[a] OR and 95% CI were estimated using unconditional logistic regression and a joint fixed-effects model, adjusted for age, sex, race, and study center.

[b] Test of heterogeneity between study.

[c] Other B-cell lymphoma includes small B-lymphocytic NOS (n = 30), mediastinal large B-cell lymphoma (n = 28), large B-cell immunoblastic (n = 1), B-cell NOS (n = 87), Precursor B NHL (n = 27), other B NHL (n = 60), precursor B-lymphoblastic leukemia or lymphoma (n = 2), hairy cell leukemia (n = 8), and lymphoblastic lymphoma (n = 1).