ORIGINAL ARTICLES—LIVER, PANCREAS, AND BILIARY TRACT

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

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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.** ***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%.[1–3]

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.[6,7]

We present results from a large international pooled analysis of the association between non-Hodgkin lymphoma (NHL) and HCV

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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Table 1. Characteristics of Case-Control Studies Included in the Pooled Analysis

Acronym	Country: Study center	Year	Cases (n = 4784)		
			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

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).

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).[8,9] 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[10–14] 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[17,18] 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 subtype-specific 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