Hepatitis C Virus and Risk of Non-Hodgkin Lymphoma: A Population-Based Case-Control Study among Connecticut Women

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Abstract

Objective: Previous epidemiologic studies of hepatitis C virus (HCV) infection and B-cell non-Hodgkin lymphoma (B-NHL) have yielded conflicting results, perhaps due to differences in the classification of B-NHL and the choice of non-population-based control groups that may not reflect the background population prevalence of HCV. To further investigate the link between HCV and NHL, we conducted HCV testing on serum samples of 998 women (464 cases; 534 controls) from a population-based case-control study of women in Connecticut. Methods: Serum samples were screened for HCV antibodies using an enzyme immunoassay; positive samples were confirmed by additional testing for HCV antibodies and for serum HCV RNA. Results: Approximately 2% (8 of 464) of cases and 1% (5 of 534) of controls tested positive for HCV. The risk of NHL associated with HCV infection appeared to be concentrated among B-cell lymphomas [odds ratio (OR) 2.0; 95% confidence interval (CI) 0.6, 8.2], particularly among follicular lymphomas (OR 4.1, 95% CI 0.8, 19.4). Conclusion: The primary strength of this study is our use of a population-based study design, although the low prevalence of HCV among women in Connecticut resulted in wide CIs for the estimated association between HCV and B-NHL subtypes. Our study suggests that HCV may be associated with increased risk of development of B-NHL, and that this risk may vary by B-NHL subtype among women. Due to the relatively low prevalence of HCV in our study population and the scarcity of population-based epidemiologic research on this subject, our study highlights the need for additional large, population-based studies of the role of HCV in the etiology of B-NHL. (Cancer Epidemiol Biomarkers Prev 2004;13(3):425–430)

Introduction

Although incidence rates of non-Hodgkin lymphoma (NHL) have increased dramatically over the past several decades throughout the world, the etiology of NHL remains largely unknown (1). Epidemiologic studies have proposed a link between hepatitis C virus (HCV) infection and both benign and malignant lymphoproliferative diseases, including mixed cryoglobulinemia (2–25). MC is a systemic vasculitis often characterized as ''benign'' B-cell proliferation, which is thought to progress to B-cell NHL (B-NHL) in 5–10% of patients (26–28). Because an estimated 40–100% of patients with MC are chronically infected with HCV (26–28), much of the research on the potential role of HCV in the etiology of NHL has focused solely on B-cell malignancy. A study of the clinical features of B-NHL among HCV+ and HCV− patients suggested that HCV may impact only a subset of B-NHLs (29). However, previous epidemiologic studies of HCV and B-NHL have yielded conflicting results, perhaps due to differences in HCV prevalence, the classification of B-NHL, or the choice of comparison population.

B-NHLs represent a heterogeneous group of lymphomas that may be categorized according to the WHO classification system (30). Before the introduction of the WHO system, the Working Formulation (WF) was used to categorize NHL according to histologic type (diffuse, follicular), tumor grade (low, intermediate, high), and immunologic type (B cell, T cell). If HCV infection is associated predominantly with one NHL subtype, previous epidemiologic research that combined T-cell NHL (T-NHL) and other lymphoproliferative diseases with B-NHL, used the WF classification system, or did not consider B-NHL subtype (2–4, 6–8, 10–14, 16, 18, 20–24) may have underestimated the role of HCV in the etiology of NHL.

Much of the previous epidemiologic research has also suffered from critical methodological limitations in the

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Note: Certain data used in this study were obtained from the Connecticut Tumor Registry of the Connecticut Department of Public Health. The authors assume full responsibility for analyses and interpretation of these data.

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choice of a comparison population that is unlikely to reflect the true underlying population prevalence of HCV, creating uncertainty about the relationship between HCV and NHL. While approximately 3% of the world population, representing 170 million people, is chronically infected with HCV, the prevalence of HCV infection varies by geographic region and population subgroup from less than 0.5% to more than 20% (31, 32). Due to the variation in HCV prevalence in different populations, it is essential to compare HCV prevalence among NHL cases to a control group that accurately reflects the background prevalence of HCV in the population, which is particularly challenging in hospital- and clinic-based case-control studies. To our knowledge, no large, population-based report of the role of HCV in the etiology of NHL and NHL subtypes has been published.

Because rates of NHL have increased dramatically in recent years for unknown reasons (1), understanding the potentially etiologic role of HCV in the development of NHL is crucial. On the basis of the paucity of population-based epidemiologic studies that consider risk of B-NHL subtypes, we evaluated the link between HCV and NHL in a population-based case-control study of women in Connecticut.

Materials and Methods

Study Population. Subjects for this population-based case-control study were recruited among women in Connecticut from 1995 to 2001. The Yale Comprehensive Cancer Center's Rapid Case Ascertainment Shared Resource (RCA), a component of the Connecticut Tumor Registry (CTR), was used to identify incident cases of NHL [International Classification of Diseases (ICD)-O, M-9590–9595, 9670–9687, 9690–9698, 9700–9723]. The CTR is a population-based tumor registry that receives reports of cancer cases from licensed hospitals and clinical laboratories in Connecticut, neighboring states, and Florida to ensure complete case ascertainment. Members of the RCA field staff are responsible for actively surveying all non-pediatric Connecticut hospitals to identify newly diagnosed cases in a timely fashion. To be eligible for this study, identified cases of NHL were required to be female residents of Connecticut who were between the ages of 21 and 84 at the time of diagnosis, with no previous diagnosis of cancer (except non-melanoma skin cancer), and who were alive at the time of the interview. A total of 1122 potential NHL cases was identified, of which 290 were ineligible for the study (167 died before interview, and 123 were excluded for other reasons, such as previous cancer diagnosis, or inability to speak English). A total of 832 incident cases of NHL fulfilling the eligibility criteria was contacted for participation in this study, of whom 601 (72%) completed in-person interviews. The median time between diagnosis and interview for cases was 2.5 months.

Histologic confirmation of NHL for each case was conducted on tissue samples obtained from the pathology department where the case was diagnosed. Two study pathologists (Drs. Flynn and Tallini) independently reviewed and classified each tissue sample by NHL subtype according to the WHO classification scheme (30). Tissue samples receiving conflicting classifications were reevaluated until the study pathologists reached agreement.

A population-based control group of female residents of Connecticut, aged 21–84, was assembled using two methods. Random digit dialing was used to contact women less than 65 years of age. Including the initial telephone screening, 69% of the women contacted using random digit dialing participated in the study. Women 65 years of age and older were selected randomly from the files of the Centers for Medicare and Medicaid Services; 47% of these women participated in the study. Controls were frequency matched to cases by age within 5-year groups by adjusting the number of controls randomly selected within each age stratum every few months. In-person interviews were completed for a total of 718 controls.

Data Collection. After obtaining physician approval, all cases were approached first by letter and then by telephone. A study nurse administered a standardized, structured questionnaire and obtained a serum sample from those subjects who agreed to participate. Serum samples for HCV testing were available for 77.2% (464 of 601) of interviewed cases and 74.4% (534 of 718) of interviewed controls. In this case-control study, subjects for whom the blood draw was contraindicated, or who refused to participate in the blood-draw, were offered the option to provide buccal-cell brushing samples instead. During the interview, respondents were asked to provide demographic information and data on a number of known or suspected risk factors for NHL.

The study protocol was approved by Institutional Review Boards of Yale University and the Connecticut Department of Health. HCV testing, described below, was performed after samples had been delinked from uniquely identifying personal information.

Laboratory Methods. Samples were stored at −70°C for 1–4 years before testing. Each sample was assigned a unique, random identification number to blind the laboratory with respect to the disease status of the sample. Serum samples were screened for HCV antibodies with a third generation enzyme immunoassay (Ortho, Raritan, NJ), estimated to have 97–99% sensitivity and >99% specificity (33). Positive samples were tested further for serum HCV antibodies with a third generation radio-immunoblot assay (RIBA, Ortho) and for serum HCV RNA using the Amplicor assay (version 2.0, Roche Diagnostics, Indianapolis, IN). Samples were considered to be HCV-positive if either the RIBA or Amplicor results were positive.

Statistical Analysis. Statistical analyses were performed using the SAS system, version 8.02 (SAS Institute, Inc., Cary, NC). Age, race, education, body mass index (BMI), family history of cancer, history of alcohol consumption, and history of blood transfusion (including number, age, and year of transfusion) were considered as potential confounders of the relationship between HCV and NHL and as possible predictors of HCV status (see categories in Table 1). Continuous variables were categorized *a priori* based on previous cutpoints used in the literature (BMI, education, number, and year of blood transfusions) or the distribution among controls (age at diagnosis/interview, age at blood

Table 1. Selected characteristics of NHL cases (*N* = 464) and controls (*N* = 534) among Connecticut women

	Cases *N* (%)	Controls *N* (%)
Age (years) (χ^2 = 1.22, *P* = 0.75)		
<55	139 (30.0)	159 (29.8)
55–64	107 (23.1)	110 (20.6)
65–74	125 (26.9)	147 (27.5)
≥75	93 (20.0)	118 (22.1)
Race (χ^2 = 3.37, *P* = 0.50)		
White	447 (96.3)	507 (94.9)
Black/AA	12 (2.6)	14 (2.6)
Other	5 (1.1)	13 (2.4)
Education (χ^2 = 5.75, *P* = 0.06)		
High School or less	184 (39.7)	198 (37.1)
Some College	158 (34.1)	159 (29.8)
College Graduate or more	122 (26.3)	177 (33.2)
BMI (kg/m^2) (χ^2 = 3.83, *P* = 0.15)		
<25	232 (50.0)	300 (56.2)
25–29.99	152 (32.8)	152 (28.5)
≥30	80 (17.2)	82 (15.4)
Family history (χ^2 = 5.23, *P* = 0.07)		
No cancer among first degree relatives	96 (20.7)	128 (24.0)
NHL	9 (1.9)	3 (0.6)
Other cancer	359 (77.4)	403 (75.5)
Alcohol (χ^2 = 1.28, *P* = 0.26)		
Nondrinker	167 (36.0)	174 (32.6)
Drinker	297 (64.0)	360 (67.4)
Blood transfusion (χ^2 = 0.84, *P* = 0.36)		
Never	342 (73.7)	407 (76.2)
Ever	122 (26.3)	127 (23.8)

transfusions). Associations between potential confounders and NHL were assessed using Pearson's χ^2 statistic; due to the low prevalence of HCV in our study population, associations between these variables and HCV status were assessed using Fisher's exact test and the Cochran-Armitage test for linear trend among the categories (34). Unconditional logistic regression models were developed using data on HCV status to predict the risk of NHL and NHL subtypes (35). Inclusion of potential confounders both individually and in groups in multivariate unconditional logistic regression models did not result in a material change (>10%) in the estimated odds ratios (ORs); therefore, unadjusted ORs and confidence intervals (CIs) are presented. On the basis of the low prevalence of HCV in our study population, the exact method, rather than the more common logit method, was used to calculate more conservative CI estimates for all ORs (34).

Results

Selected characteristics of cases and controls were compared (Table 1). Because controls were frequency matched to cases by age within 5-year groups, the age distribution among cases and controls was similar. In addition, cases and controls were similar with respect to race, BMI, history of alcohol consumption, and history of blood transfusion. However, cases were somewhat more likely than controls to have completed fewer years of education and report a family history of NHL and other cancers among first degree relatives.

Approximately 2% (8 of 464) of cases and 1% (5 of 534) of controls tested positive for HCV (OR 1.9; 95% CI 0.5, 7.3; Table 2). Predictors of HCV status among the population-based group of controls were examined (data not shown). Among controls, higher HCV prevalence was non-significantly associated with younger age (4 of 269 = 1.5% among women less than 65 years old *versus* 1 of 265 = 0.3% among women 65 years of age or more; *P* = 0.37) and non-white race (4 of 503 = 0.8% among white women *versus* 1 of 26 = 3.8% among non-white women, *P* = 0.23). Among controls, HCV was not related to transfusion history (ever had transfusion, transfusion before 1990 *versus* after 1990; data not shown).

Due to the heterogeneity of lymphomas that comprise NHL, the association between HCV and NHL was further investigated by NHL subtypes, classified according to the WHO classification scheme. These data suggest that the risk of B-cell NHL may be associated with HCV infection (OR 2.0; 95% CI 0.6, 8.2). In addition, the effect of HCV appeared to be concentrated in certain

Table 2. Risk of NHL and NHL subtypes associated with HCV among Connecticut women

	Number of subjects			
	HCV− (%)[a]	HCV+ (%)[a]	OR	95% CI[b]
Controls	529 (99.1)	5 (0.9)	1.0	
Cases	456 (98.3)	8 (1.7)	1.9	(0.5, 7.3)
Immunologic type				
B cell	362 (98.1)	7 (1.9)	2.0	(0.6, 8.2)
T cell	34 (100.0)	0 (0.0)		
Other	60 (98.4)	1 (1.6)	1.8	(0.0, 16.1)
WHO subtype[c]				
CLL	43 (97.7)	1 (2.3)	2.5	(0.1, 22.7)
DLBCL	133 (98.5)	2 (1.5)	1.6	(0.1, 9.8)
FL	103 (96.3)	4 (3.7)	4.1	(0.8, 19.4)
FL tumor grade				
Low	45 (97.8)	1 (2.2)	2.4	(0.0, 21.6)
Intermediate	41 (95.3)	2 (4.7)	5.2	(0.5, 32.6)
High	16 (94.1)	1 (5.9)	6.6	(0.1, 63.8)
			P for linear trend < 0.01	

[a](%) represents row percentages.
[b]95% CIs were calculated using the exact method.
[c]CLL = chronic lymphocytic leukemia/lymphoma; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma.

subtypes of B-NHL, particularly follicular lymphoma. Among follicular lymphomas, our data suggest that HCV infection may be related to tumor grade, with the highest risk among high-grade follicular lymphomas, although this finding is based on a small number of infected cases. Inclusion of NHL risk factors and HCV predictors in multivariate unconditional logistic regression models did not materially change the estimated ORs (data not shown).

Discussion

In this population-based case-control study among women in Connecticut, we found that infection with HCV was associated with an increased risk of B-NHL, particularly among follicular lymphomas, although this finding is based on a small number of infected cases.

Our study results differ from previously published studies because they are based on the use of a population-based study design in a female study population with low HCV prevalence. Despite these differences in study design and population, our results demonstrating an increased risk of follicular lymphoma are in agreement with two hospital-based studies of B-NHL in Italy (5, 15). In addition, an increased risk of both follicular lymphoma and CLL was observed in a hospital-based study of patients with lymphoproliferative diseases in Italy (9). These and other studies have also suggested an increased risk of other B-NHL subtypes associated with HCV infection that was not observed in our study, including neoplasms of mucosa-associated lymphoid tissue (MALT) (5, 17, 19), lymphoplasmacytoid lymphoma (9, 17, 25), diffuse large B-cell lymphoma (9, 15, 17, 19, 25), mantle cell lymphoma (9), and marginal zone B-cell lymphoma (9, 15, 25). Thus, it remains unclear whether the association with HCV is restricted to particular subtypes of B-NHL. It is possible that the variably increased risk of diverse B-NHL subtypes observed in different studies is due to small sample sizes that limit power to evaluate the association by disease subtype or the use of case series or hospital-based study designs rather than a population-based study design.

Other epidemiologic studies of HCV and NHL that have used the WF to classify NHL subtypes have yielded conflicting results. Four studies reported that the risk of NHL associated with HCV infection did not vary by WF subtype (8, 10, 14, 21). However, two studies reported an increased prevalence of HCV among patients with low-grade lymphoma (6, 16), while two other studies reported an increased prevalence of HCV among patients with intermediate-grade lymphoma (2, 22). The variation in these observations may be due to differences in geographic location and the choice of study design, and because the WF does not classify lymphomas by histology and tumor grade simultaneously.

The main limitation of most previous studies of HCV and NHL may be the use of a comparison population that may not accurately reflect the background prevalence of HCV in the population, creating uncertainty about the relationship between HCV and NHL. Several previous studies of HCV and NHL have not used a comparison population (3, 4, 7, 15, 16), while others have compared case patients to blood donors (8, 10, 11, 22), various clinical populations (2, 5, 6, 8, 10–14, 17, 19, 21, 25), or healthy populations without a defined sampling method (2, 5, 6, 8, 9, 13, 19, 23). Moreover, a recent population-based study of HCV prevalence in the United States, based on screening serum samples from the third National Health and Nutrition Examination Survey, suggested that clinical populations or blood donors may not accurately reflect the prevalence of HCV (36).

The primary strength of this study is our use of a population-based study design. Several arguments suggest that this design allowed us to more accurately estimate the role of HCV in the etiology of NHL than previous, non-population-based studies. First, our case group consisted of a population-based sample of histologically confirmed, incident cases of NHL, rather than a series of prevalent cases, which minimized selection and survivor bias. Second, we used a population-based control group, frequency-matched to cases by age, which allowed us to directly compare the prevalence of HCV among women with NHL to comparable women from the same population. Selected demographic characteristics of our study population were related to HCV positivity, including age less than 65 years old and non-white race, although the small sample size limited our ability to explore additional predictors of HCV status. A 1999 study of HCV prevalence in the United States reported a similar magnitude relationship between these demographic characteristics and HCV positivity (36). In addition, only histologically confirmed, incident cases were included in the study sample to minimize information bias resulting from disease misclassification.

The main limitation of this population-based study is the low prevalence of HCV among women in Connecticut, resulting in wide CIs for the estimated association between HCV and B-NHL subtypes. However, the consistency of our results with those from several other studies (5, 9, 15, 17, 19), particularly those reporting an increased risk of follicular lymphoma and CLL (5, 9, 15), suggests that the low prevalence in our population affected only the precision of our results. We used an exact method to calculate conservative CI estimates for all ORs, to appropriately take into account the low prevalence of HCV in this population. Future population-based studies of the relationship between HCV and B-NHL should be conducted in areas with higher HCV prevalence, or with a larger sample size in geographic regions with low HCV prevalence.

Although the screening enzyme immunoassay used in this study generally has high sensitivity (97–99%) and specificity, it may be less sensitive in detecting HCV infection in patients with varying degrees of immunosuppression than in immunocompetent individuals (37). Given the likelihood of impaired immune function among NHL patients, we may have underestimated the prevalence of HCV among the cases in our study population, thus underestimating the association between HCV and NHL. We were able to conduct HCV testing on only three-quarters (998 of 1319) of the serum samples of women who participated in the original population-based case-control study. However, it is unlikely that the use of a portion of the total study population resulted in biased estimates of the role of HCV in the etiology of NHL because the distributions

of demographic characteristics and NHL risk factors for the sample of women included in this study were similar to the distributions for the entire study population (data not shown).

The mechanisms by which HCV may induce NHL are unclear. Recently, a persistently HCV-infected B-cell line was established from a patient with MC (38). However, other studies have failed to detect the presence of HCV RNA in the majority of NHL tumor cells (39, 40), arguing against a direct role for HCV in lymphomagenesis. Along these lines, it has been hypothesized that HCV infection may provide an exogenous trigger for antigen-driven clonal B-cell expansion, favoring malignant transformation (39, 41–46). The E2 envelope protein of HCV can bind to CD81, a cell surface protein present on B lymphocytes, which provides a potential mechanism for B-cell stimulation by HCV (47, 48).

A role of HCV in the etiology of NHL is further supported by evidence of the effects of antiviral therapy. Complete remission of splenic lymphoma was observed among HCV+ patients following treatment with IFN-α, while no effect of the treatment was observed among HCV− patients with splenic lymphoma (49). Similarly, rearrangement of immunoglobulin genes and t(14;18) translocation, both hallmarks of HCV infection that are also associated with lymphoma development, were reversed with IFN-α-based treatment (50).

In summary, our study suggests that HCV may be indirectly involved in the development of B-NHL, and that this risk may vary by B-NHL subtype among women. Due to the relatively low prevalence of HCV in our study population and the scarcity of population-based epidemiological research on this subject, our study highlights the need for additional large, population-based studies of the role of HCV in the etiology of B-NHL.

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