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Hepatitis C virus and risk of non-Hodgkin lymphoma in British Columbia, Canada

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We investigated Hepatitis C virus (HCV) seropositivity and the risk of non-Hodgkin lymphoma (NHL) in a population-based case-control study in British Columbia, Canada. Cases were aged 20–79, diagnosed between March 2000 and February 2004, and resident in greater Vancouver or Victoria. Cases with HIV or a prior transplant were excluded. Controls were chosen from the Client Registry of the British Columbia (BC) Ministry of Health, and were age/sex/region frequency matched to cases. Antibodies for HCV were measured in 795 cases and 697 control subjects. HCV seropositivity was 2.4% in cases and 0.7% in controls [odds ratio (OR) = 2.6, 95% confidence interval (CI) = 0.9–7.4]. A significantly elevated risk was observed for B-cell lymphoma (OR = 2.9, 95%CI = 1.0–8.6). The highest risks were associated with diffuse large B-cell lymphoma (OR = 7.3, 95%CI = 2.1–25.0) and marginal zone lymphoma (OR = 6.1, 95%CI = 1.1–33.9). Our results provide further evidence that HCV infection contributes to NHL risk.

Key words: non-Hodgkin lymphoma; virus; hepatitis; hepatitis C; epidemiology; etiology

The incidence of non-Hodgkin lymphoma (NHL) has been rising steadily for the past 30 years, but has leveled off in recent years.[1,2] Hepatitis C virus (HCV) infection is well-known to be the primary risk factor for type II mixed cryoglobulinemia (MC).[3,4] MC is a nonmalignant lymphoproliferative condition, which may evolve into B-cell NHL in 5–8% of cases.[5] This possible association between HCV infection and NHL was first suggested in 1993.[6] The epidemiologic evidence concerning this potential association was recently reviewed.[7] Overall, there was a 2-fold risk of NHL associated with HCV, but there was significant heterogeneity found between studies based on study design and HCV prevalence. Higher risks were found with case-control studies particularly those using hospital controls and in studies in high HCV prevalence areas.

HCV was first identified in 1989, and was known as "NonA, NonB Hepatitis" to describe inflammatory liver disease not attributable to infection with Hepatitis A or Hepatitis B.[8] The World Health Organization estimates there are 170 million people, around 3% of the world's population, infected with hepatitis C, with 3–4 million new infections per year.[9] In Canada, it is estimated that there are ~250,000 people (0.8%) infected with hepatitis C and that as few as 30% of those who have hepatitis C know they are infected.[10] The prevalence of HCV infection in British Columbia (BC) is estimated to be 1.5%, nearly twice the national rate, likely due to a high rate of injection drug use (IDU).[11,12]

To further investigate the association between HCV infection and NHL in a low prevalence area, we examined data from a population-based case-control study in BC, Canada.

Material and methods

Study population

The methodology has been described previously.[13] Between March 2000 and February 2004, NHL cases from the Greater Vancouver Regional District (GVRD) and the Capital Regional District (CRD), which includes the city of Victoria, were enrolled from the BC Cancer Registry. Cases included subjects with newly diagnosed NHL aged 20–79 without evidence of HIV infection. Population controls were frequency matched to cases by sex, age (within 5-year age group), and residential location (GVRD or CRD) in an ~1:1 ratio. Controls were selected from the Client Registry of the BC Ministry of Health, which contains information on subscribers to the provincial health insurance plan.

Study material was made available in the 4 most commonly spoken languages in the catchment area, English, Chinese, Punjabi and Tagalog. Subjects were asked to complete a questionnaire and provide a blood or saliva sample. Questionnaires were completed by self-report and a computer-assisted telephone interview (CATI). Questionnaires contained information on demographic characteristics, sunlight exposure, medical history, and other factors. Among eligible subjects who we were able to contact, 79% of cases and 46% of controls agreed to participate.

Written informed consent was obtained from each participant. The study was approved by the BC Cancer Agency-University of BC Research Ethics Board. All cases were reviewed and coded using the World Health Organization classification.[14] Final pathological grouping was done according to the InterLymph classification.[15]

HCV

This study of HCV risk included cases that had an HCV test in BC or had sufficient plasma to ascertain HCV seropositivity. From all sources, HCV seropositivity was determined for a total of 795 (96.0%) cases and 697 (82.2%) controls.

A database containing the results of all HCV tests in BC since 1992 is maintained by the BC Centre for Disease Control (BCCDC). HCV testing is recommended for all newly diagnosed NHL cases.[16] For standard HCV testing in BC, primary screening was performed by Abbott AxSYM HCV 3.0, and reactive samples were retested by Ortho Vitros Eci HCV 3.0. HCV seropositivity results were obtained from the BCCDC database for 458 (55.3%) cases and 93 (11.0%) controls. For cases, testing occurred a median of 34 days after diagnosis (interquartile range 17–65 days after diagnosis), and for controls the testing occurred a median of 821 days prior to the referent date (interquartile range 63–1,580 days prior to the referent date).

Cases and controls with sufficient plasma and either not linked to the BCCDC database or with an equivocal result from the BCCDC database (3 cases) were tested for HCV seropositivity. In

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addition, 101 subjects with an HCV serology result in the BCCDC laboratory database were also tested for HCV seropositivity in plasma. A total of 1,045 plasma samples were tested for HCV seropositivity. Blood samples were obtained a median of 61 days after diagnosis/referent date (interquartile range 24–134 days).

The HCV serology testing was performed at either the National Microbiology Lab (NML) in Winnipeg, Manitoba (467 samples) or the BCCDC in Vancouver, BC (578 samples). At the NML, primary screening was performed by Abbott HCV EIA v.2.0, and reactive samples were retested by Innogenetics (Inno-Lia HCV Ab III Update). At the BCCDC primary screening was performed by Bayer ADVIA Centaur HCV and reactive samples were retested with Abbott Architect anti-HCV. Samples were considered antiHCV equivocal when only one EIA was reactive. Only samples reactive by both tests were considered to be HCV seropositive.

Of the 101 subjects with a nonequivocal HCV determination in both the BCCDC database and by serology, 96 were negative on both, 4 were positive on both and 1 was positive on serology, but negative in the BCCDC database. The concordance rate was 99.0% (95%CI (94.6–100.0%). All 3 cases recorded as "equivocal" in the BCCDC database were negative by serology, and were considered negative for all analyses.

Statistical analyses

The odds ratio (OR) and 95% confidence interval (CI) for the risk of NHL for HCV seropositivity was estimated using logistic regression. The change-in-estimate criterion was used to select confounders with a 5% relative change in the OR considered important.[17] The possible confounders examined included the matching factors (age, sex and region) factors, which may differ due to response bias (ethnicity and education level); known NHL risk factors (family history of NHL); and possible means of HCV transmission (prior history of IDU, tattooing, piercing and blood transfusion). Only the removal of IDU changed the OR for HCV seropositivity more than 5%. To allow comparisons between previous results, unadjusted ORs and ORs adjusted for IDU are presented.

Interactions between HCV seropositivity and the potential confounding variables were examined by entering the interaction term into the logistic regression model. Significance was based on the likelihood ratio p-value for the interaction term.

Sub-group analyses of the association between HCV seropositivity and NHL were also performed for histological subtypes. Diffuse large cell lymphoma, follicular lymphoma and marginal zone lymphoma were the 3 largest subtypes and were analyzed as individual sub-groups. All T-cell and all B-cell tumors were examined, as well as other B-cell (nondiffuse large cell, nonfollicular, nonmarginal zone). A test for heterogeneity between histologic subtypes was performed by analysis of the case group only using polychotomous logistic regression.[18,19]

Results

The study characteristics are shown in Table I. Cases and controls were similar with respect to age, sex, region, education, ethnicity, piercing and tattooing. An increased risk of NHL was seen in those reporting IDU (OR = 3.63 95% CI = 1.17–11.2) and prior blood transfusion (OR = 1.62 95% CI = 1.24–2.11). Elevated, but nonsignificant ORs were observed for family history of NHL (OR = 1.71 95% CI = 0.98–2.99) and self-reported HCV infection (OR = 3.04 95% CI = 0.79–11.6).

HCV seropositivity rates were similar with regard to region, education, ethnicity, family history of NHL, piercing and blood transfusion. A higher prevalence of HCV seropositivity was observed for males compared to females (20/837 (2.4%) vs. 4/655 (0.6%), $p + 0.007$), and in younger subjects compared to older (19/671 (2.8%) vs. 5/821 (0.6%), $p = 0.001$). The mean age of the seropositive subjects was 53.4 years compared to 60.0 years for the seronegative subjects ($p = 0.006$). There was much higher proportion of HCV seropositivity in ever injection drug users compared to non users (9/18 (50.0%) vs. 14/1428 (1.0%), $p < 0.001$). There was also a higher rate of HCV seropositivity in individuals who had tattoos compared to those without tattoos (7/88 (8.0%) vs 16/1365 (1.1%), $p < 0.001$).

Of the 24 subjects with a positive HCV test, only 9 self-reported an HCV diagnosis. An additional 3 subjects reported hepatitis exposure, but of unknown type, and 1 individual did not answer the question.

Overall, there was a significant association between HCV seropositivity and NHL, with HCV seropositive subjects having an unadjusted OR of 3.39 (95% CI = 1.26–9.12) compared to subjects with negative serology (Table II). After adjustment for IDU, the OR for was elevated, but no longer statistically significant (OR = 2.57, 95% CI = 0.89–7.44). A larger risk was associated with B-cell tumors (OR = 3.56, 95% CI = 1.13–9.65) than T-cell tumors (OR = 1.80, 95% CI = 0.21–15.6), although this difference was not significant (p-value for heterogeneity >0.25). After adjustment for IDU, the risk of HCV for B-cell tumours remained statistically significant (OR = 2.94, 95% CI = 1.00–8.58).

There was significant heterogeneity among the 4 B-cell subgroups ($p < 0.001$) primarily due to the lack of an elevated risk for follicular lymphoma. The largest increased risks associated with HCV were observed for diffuse large cell lymphoma (OR = 8.30, 95% CI = 2.89–23.8) and marginal zone lymphoma (OR = 4.51, 95% CI = 1.06–19.2). Similar risks were observed after adjustment for IDU (diffuse large cell, OR = 7.31 95% CI = 2.14–25.0; marginal zone OR = 6.08 95% CI = 1.09–33.9). There were no follicular lymphoma cases with HCV seropositivity.

No significant interactions were observed between HCV seropositivity and sex, age, region, education, family history of NHL or prior history of IDU, piercing, or tattoo. There was a significant interaction for ethnicity (p interaction = 0.008). After adjustment for IDU, the OR for Caucasians was 4.22 (95% CI = 1.16–15.3) and for non-Caucasians was 0.23 (95% CI = 0.01–4.47).

Discussion

This study provides further evidence that HCV infection is associated with the risk of NHL. We found that the risk of NHL was over 3 times greater in HCV seropositive subjects compared to seronegative subjects. Our results are consistent with the results of the resent meta-analysis by Dal Maso and Franceschi.[7] We found unadjusted ORs of 3.4, 3.6 and 1.8 for all NHL, B-cell and T-cell lymphomas, whereas the meta-analysis calculated ORs of 2.5 for all NHL, 2.7 for the major B-cell subtypes (diffuse large cell and follicular) and 1.5 for T-cell lymphomas.

The risk according to NHL subgroups in our study differs somewhat from the meta-analysis. Our finding that the highest risk was observed in the diffuse large cell and marginal zone B-cell lymphoma agrees with those of the meta analysis, however, we found no association with follicular lymphoma whereas the meta analysis found an overall 2.7-fold increased risk for follicular lymphoma.

We found that the OR for risk of NHL remained high after adjustment for IDU, providing some evidence that HCV is the primary etiologic factor rather than some other agent associated with IDU. There was a larger effect among Caucasians than nonCaucasians, however, the number of non-Caucasians in our study was small. No HCV seropositive cases or controls were seen in Asian subjects, the largest non-Caucasian subgroup.

The causal role of HCV infection in the etiology of NHL is supported by the evidence that splenic marginal zone lymphomas regressed in HCV seropositive patients following treatment with interferon, while the treatment of HCV noninfected patients showed no effect.[20] The presence of HCV antigens in lymphoma tissue further supports this role.[21] However, the mechanisms by which HCV is involved in lymphomagenesis, are still unknown. Since HCV is lymphotropic, a direct oncogenic role has been

TABLE I – CHARACTERISTICS [FREQUENCY (%)] OF CASES AND CONTROLS AND HCV SEROPOSITIVITY

	Cases number (%)	Controls number (%)	OR	95% CI
Total	795	697		
Sex				
Male	463 (58.2)	374 (53.7)		
Female	332 (41.8)	323 (46.3)		
Age				
20–49	158 (19.9)	173 (24.8)		
50–59	191 (24.0)	149 (21.4)		
60–69	208 (26.2)	187 (26.8)		
70+	238 (29.9)	188 (27.0)		
Region				
GVRD (Greater Vancouver)	661 (83.1)	525 (75.3)		
CRD (Greater Victoria)	134 (16.9)	172 (24.7)		
Education				
Less than high school	146 (18.4)	98 (14.1)	1.00	
High school graduate	414 (52.1)	386 (55.4)	0.77	(0.58–1.01)
University graduate	217 (27.3)	205 (29.4)	0.76	(0.56–1.04)
Unknown	18 (2.3)	8 (1.1)		
Ethnicity				
Caucasian	629 (79.1)	570 (81.8)	1.00	
Asian	74 (9.3)	55 (7.9)	0.83	(0.60–1.15)
South Asian	27 (3.4)	27 (3.9)	0.66	(0.40–1.07)
Other/mixed	37 (4.7)	26 (3.7)	1.20	(0.74–1.95)
Unknown	28 (2.7)	19 (2.7)		
Family history of NHL				
No	752 (94.6)	677 (97.1)	1.00	
Yes	34 (4.3)	19 (2.7)	1.71	(0.98–2.99)
Unknown	9 (1.1)	1 (0.1)		
Self-reported HCV				
No	734 (92.3)	671 (96.3)	1.00	
Yes	8 (1.0)	2 (0.3)	3.04	(0.79–11.6)
Unknown	53 (6.7)	24 (3.4)		
Ever injection drug use				
No	744 (93.6)	684 (98.1)	1.00	
Yes	14 (1.8)	4 (0.6)	3.63	(1.17–11.2)
Unknown	37 (4.7)	9 (1.3)		
Ever blood transfusion				
No	594 (74.7)	576 (82.6)	1.00	
Yes	161 (20.3)	102 (14.6)	1.62	(1.24–2.11)
Unknown	40 (5.0)	19 (2.7)		
Ever Piercing				
No	462 (38.1)	389 (55.8)	1.00	
Yes	303 (58.1)	304 (43.6)	1.18	(0.85–1.64)
Unknown	30 (3.8)	4 (0.6)		
Ever Tattoo				
No	715 (89.9)	650 (93.3)	1.00	
Yes	46 (5.8)	42 (6.0)	1.12	(0.73–1.72)
Unknown	34 (4.3)	5 (0.7)		

TABLE II – HCV ASSOCIATION WITH NHL

Pathologic subtype	Cases[1]	OR[2]	95%CI	Cases with known history of IDU[3]	OR[4]	95%CI
All NHL	19/776	3.39	1.26–9.12	18/740	2.57	0.89–7.44
All B-cell	18/699	3.56	1.13–9.65	17/665	2.94	1.00–8.58
Diffuse large cell	12/200	8.30	2.89–23.8	11/194	7.31	2.14–25.0
Follicular	0/212	0	0.00–3.59[5]	0/199	0	–
Marginal zone	3/92	4.51	1.06–19.2	3/83	6.08	1.09–33.9
Other B-cell	3/195	2.13	0.50–8.99	3/189	1.59	0.32–8.00
All T-cell	1/77	1.80	0.21–15.6	1/75	0.37	0.02–6.06

[1]HCV seropositive/HCV seronegative, controls 5/692.–[2]Unadjusted odds ratio.–[3]HCV seropositive/HCV seronegative, controls 5/683.–[4]Adjusted for injection drug use (IDU).–[5]Confidence interval estimated by conditional maximum likelihood estimation.[17]

hypothesized,[22] however, since HCV is an RNA virus without DNA intermediates, it cannot be integrated into the host genome, and must induce malignancies with indirect mechanisms.[23]

HCV-related NHL arise after a long time of infection, so it may be that persistence of the virus in lymphocytes results in chronic stimulation of B-cells.[24] The identification of somatic mutations in immunoglobulin-variable region genes expressed by B-cell NHL indicative of an antigen selection process supports this hypothesis.[25] In addition, the HCV envelope protein E2 is able to bind to CD81, a B-cell receptor. The stimulation of the CD81 complex enables B-cells to respond to lower concentrations of antigen and facilitates B-cell proliferation.[26] Finally, the $t(14; 18)$ translocation has been shown to be present in a significant percentage of peripheral blood lymphocytes in HCV infected individuals, particularly with MC.[27] This translocation is responsible for BCL-2 activation, which extends B-cell survival by inhibiting apoptosis.[28]

The major strengths of this study are the large size, and the fact that the cases and controls are population based. Our study is by

far the largest Canadian study, with over 7 times the number of cases as either of the 2 previous Canadian studies, which utilized clinic based lymphoma cases and convenience controls (health care workers or blood donors).[29,30] Also, NHL cases with HIV or prior transplant were excluded, thus eliminating potential bias in the risk estimates from the associations of these factors with NHL and HCV infection. In addition, questionnaire information on other high-risk activities was collected.

The study has several potential weaknesses. Despite the relatively large sample size, the study still has limited power to detect associations for specific NHL subtypes, or to detect interactions. Another limitation of the study was that the high rate of nonresponse could have introduced bias if cases and controls differentially participated based on their knowledge of prior HCV infection. It is possible that controls who engaged in high-risk activity such as IDU may not have chosen to participate. However, the estimates of risk for HCV infection did not change after adjusting for education, history of IDU, tatooing or blood transfusion. Although the NHL risk for HCV infection remained after adjustment for IDU, since IDU use is likely subject to misclassification error, we cannot rule out the possibility of residual confounding.

The use of both prior HCV testing results and blood samples taken after diagnosis could also have biased the results. Subjects who tested negative for HCV serology from the BCCDC database could have seroconverted after testing but prior to diagnosis/referent date. In controls, this would lead to an upwardly biased estimate of risk. This bias is likely to be small as the number of controls identified from the database was small (11% of total), and the HCV positivity rate in controls is extremely low. Another possible source of bias is that positive results from serology testing of the study plasma samples may reflect seroconversion after diagnosis, however, there was a relatively short time interval between diagnosis and blood draw (median 24 days).

In conclusion, our study provides further support for the association between HCV infection and risk of NHL.

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