Hepatitis B Virus Infection and B-Cell Non-Hodgkin's Lymphoma in a Hepatitis B Endemic Area: A Case-control Study

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Several studies have reported a higher prevalence of chronic hepatitis C virus (HCV) infection in patients with B-cell non-Hodgkin's lymphoma and suggested a pathogenic role for HCV, but studies on hepatitis B virus (HBV) infection and non-Hodgkin's lymphoma are limited. To determine the association between HBV infection and non-Hodgkin's lymphoma, we performed a case-control study in Korea, a hepatitis B endemic area. We recruited 222 patients newly diagnosed with non-Hodgkin's lymphoma at Seoul National University Hospital between January 1997 and December 1998 as cases. Four age- and sex-matched controls were selected for each case, and the control groups comprised of 439 patients with non-hematological malignancy (control group 1) and 444 subjects with non-malignant conditions (control group 2). Relative risk of developing non-Hodgkin's lymphoma among individuals tested positive for hepatitis B surface antigen was calculated after controlling for other potential risk factors of lymphoma, such as smoking, alcohol drinking, transfusion history and HCV infection. Hepatitis B surface antigen was positive in 28 of 222 patients (12.6%) with non-Hodgkin's lymphoma compared with 32 of 439 (7.3%) in control group 1, and 21 of 444 (4.7%) in control group 2 (*P*=0.001). The crude odds ratio for B-cell non-Hodgkin's lymphoma among the HBV carriers was 2.54 (1.46–4.45) and the adjusted odds ratio was 3.30 (1.69–6.45) by multivariate analysis. The present study suggests that the risk of B-cell non-Hodgkin's lymphoma is increased in HBV carriers and warrants further investigation of the possible role of hepatitis B virus in the pathogenesis of B-cell non-Hodgkin's lymphoma.

Key words: Case-control study — Non-Hodgkin's lymphoma — Hepatitis B — Risk factor

The incidence of non-Hodgkin's lymphoma is increasing rapidly in many countries, such as the USA, UK, and Scandinavia.[1] Many factors such as immunodeficiencies, various chemical or radiation exposures and transfusion have been suggested to be risk factors, but the cause of non-Hodgkin's lymphoma remains uncertain.

Several studies in Italy and Southern California have reported a higher prevalence of chronic hepatitis C virus (HCV) infection in B-cell non-Hodgkin's lymphoma patients, ranging from 9% to 32%.[2–4] In addition, it has been hypothesized that chronic antigenic stimulation by HCV may induce the clonal expansion of immunoglobulin secreting cells and eventually lead to malignant B-cell neoplasm.[5] Like HCV, hepatitis B virus (HBV) can replicate in various extrahepatic tissues including the lymph nodes and the bone marrow.[6–8] Several studies have reported a high prevalence of HBV infection in patients with non-Hodgkin's lymphoma, ranging from 3% to 30%.[9–14] However, most of these studies were performed as case series studies without control groups.

South Korea is one of the endemic areas of chronic HBV infection, the prevalence of hepatitis B surface anti-genemia being 8.0% and 6.2% for adult males and females, respectively.[15] In comparison, the prevalence of HCV infection in the general population, in terms of anti-HCV antibody positivity, is 1.7%, which compares to that of developed countries.[16] To determine the association between HBV infection and non-Hodgkin's lymphoma, we conducted a case-control study involving a large number of patients in Korea.

MATERIALS AND METHODS

Participants All 233 patients newly diagnosed with non-Hodgkin's lymphoma at Seoul National University Hospital (SNUH) between January 1997 and December 1998 were evaluated for the study. Pathology reports were scrutinized in all cases to confirm the diagnosis. Of the initial 233 patients, 11 patients who were not tested for HBV surface antigen (HBsAg) were excluded. All of the remaining 222 patients were histopathologically classified according to the Working Formulation.[17] Immunophenotypic analysis for surface B and T lymphocytic markers was performed in 194 patients.

For each case, four controls were selected, two from patients with non-hematologic malignancy who were diagnosed at SNUH during the same period (control group 1),

and two from patients with non-malignant conditions attending SNUH during the same period (control group 2). Controls were individually matched to the lymphoma cases by age, sex, and date of admission. Patients closest in age to the case were selected. If there were more than two candidates, those who attended the hospital on the date closest to the date of case admission were selected. Control group 1 consisted of 401 patients with gastric cancer and 38 with various sarcomas including osteosarcoma, rhabdomyosarcoma, Ewing's sarcoma, primitive neuroectodermal tumor, malignant fibrous histiocytoma and was selected from 1847 gastric cancer patients and 158 sarcoma patients. Control group 2 consisted of 315 visitors and 129 patients with fracture, and was selected from 1348 visitors to the Center for Health Promotion and 238 patients who were admitted to the department of Orthopedic Surgery with the diagnosis of fracture. All visitors to the Center for Health Promotion and all the patients at the orthopedic ward received a routine check, which included a complete blood count, blood chemistry, urinalysis, fecal occult blood test, chest X-ray and electrocardiogram. Only those who were free of malignant diseases by history, physical examination and screening laboratory tests were enrolled.

In SNUH, routine viral marker screening is performed for all in-patients of the department of internal medicine and for all in-patients undergoing surgical procedure. Cases and controls were tested for HBsAg, antibodies to HBsAg, anti-HCV antibody and anti-human immunodeficiency virus (HIV) antibody by second-generation enzyme-linked immunosorbent assay using a Behring ELISA processor III (Behringwerke AG, Diagnostics, Marburg, Germany). A liver panel including total protein, serum albumin, serum alkaline phosphatase, total bilirubin, alanine aminotransferase, and aspartate aminotransferase was also obtained for all patients. Tests were performed with fresh samples on admission or during the first visit to the outpatient clinic, before any treatment, including blood transfusion or cancer chemotherapy. We reviewed medical records for information on occupation, alcohol consumption, smoking habits, previous diseases and transfusion history. For those who tested positive for HBsAg, we recorded the dates on which patients were first diagnosed as HBV carriers.

Statistical methods   The χ^2 test was used to assess the significance of differences in distribution of characteristics between cases and controls. Logistic regression analyses were performed to test the hypothesis that HBV infection may independently influence the occurrence of non-Hodgkin's lymphoma, after controlling for confounders. Confounders were used in the model if they were risk factors for non-Hodgkin's lymphoma or showed a significant association with HBV infection. Specific potential confounders were also included in the model if they had

biological plausibility as risk factors for non-Hodgkin's lymphoma. The appropriate odds ratios and their 95% confidence intervals were calculated as estimates of the association between HBV infection and non-Hodgkin's lymphoma. Statistical analysis was performed using SPSS for Windows, version 9.0 (SPSS, Inc., Chicago, IL).

RESULTS

A total of 222 cases and 883 controls were enrolled in the study. The cases consisted of 132 men (59.5%) and 90 women (40.5%) and their demographic characteristics are summarized in Table I. The cases and controls were similar with respect to sex, age, smoking, and transfusion history.

HBsAg was positive in 28 of 222 patients (12.6%) with non-Hodgkin's lymphoma, as opposed to 32 of 439 patients (7.3%) in control group 1 and 21 of 444 subjects (4.7%) in control group 2. A higher risk of non-Hodgkin's lymphoma was found in HBsAg-positive carriers than in the HBsAg-negative subjects. The odds ratios were 1.84 (1.07–3.14) versus control group 1 and 2.91 (1.61–5.25) versus control group 2. The relation of several potential confounders to non-Hodgkin's lymphoma was assessed by logistic regression analysis (Table II). The association between HBV infection and non-Hodgkin's lymphoma remained significant after controlling for age, sex, transfusion history, smoking, alcohol drinking and HCV infection (Table III).

HBsAg carrier status was not associated with any particular histologic subtypes of non-Hodgkin's lymphoma, and the HBsAg-positive rate was 13.3%, 12.9%, and 10.0% in patients with low-grade, intermediate-grade, and high-grade lymphoma. The HBsAg-positive rate was higher in B-cell lymphoma patients (14.0%) than in T-cell lymphoma patients (6.9%) in the 194 patients immunophenotyped. Subgroup analysis revealed that HBsAg-positive carriers had a higher risk of B-cell non-Hodgkin's lymphoma, but not T-cell lymphoma. The corresponding odds ratios were 2.07 (1.13–3.78) versus control group 1, and 3.27 (1.70–6.29) versus control group 2 (Table III). Eighty-two percent of B-cell non-Hodgkin's lymphoma patients had extranodal involvement and 8.1% had hepatic involvement. There was no significant difference in hepatic involvement in HBsAg-positive and -negative patients; 10.0% vs. 7.4% (P=0.65), respectively.

The HBsAg-positive rate was consistently higher for non-Hodgkin's lymphoma patients in every age group. It was highest among the younger age groups, showing a peak prevalence of 23.8% in the 20 to 29 age group, then declined with increasing age. Risk of B-cell non-Hodgkin's lymphoma was most evident in the younger HBsAg-positive groups. The odds ratios of B-cell non-Hodgkin's lymphoma were 4.66, 3.01 and 1.94 in the 29-

Table I. Characteristics of Non-Hodgkin's Lymphoma Cases and Their Age-, Sex-matched Controls, Seoul National University Hospital, Korea, 1997−1998

Characteristics	Cases (n=222)	Control 1[a] (n=439)	Control 2[b] (n=444)	P value[c]
Median age (range), yr.	52 (14–85)	52 (13–82)	52 (13–84)	1.0
Age, n (%)				1.0
≤19	9 (4.1)	13 (3.0)	18 (4.1)	
20–29	21 (9.5)	40 (9.1)	42 (9.5)	
30–39	34 (15.3)	70 (15.9)	68 (15.3)	
40–49	35 (15.8)	70 (15.9)	70 (15.8)	
50–59	52 (23.4)	104 (23.7)	105 (23.6)	
60–69	43 (19.4)	86 (19.6)	84 (18.9)	
≥70	28 (12.6)	56 (12.8)	57 (12.8)	
Sex				0.974
Male, n (%)	132 (59.5)	258 (58.8)	264 (59.5)	
Female, n (%)	90 (40.5)	181 (41.2)	180 (40.5)	
Smoking				0.078
Ever, n (%)	69 (31.1)	167 (38.0)	186 (41.9)	
Never, n (%)	130 (58.6)	245 (55.8)	235 (52.9)	
Unknown, n (%)	23 (10.4)	27 (6.2)	23 (5.2)	
Alcohol drinking				0.038
Yes, n (%)	60 (27.0)	161 (36.7)	169 (38.1)	
No, n (%)	139 (62.6)	246 (56.0)	251 (56.5)	
Unknown, n (%)	23 (10.4)	32 (7.3)	24 (5.4)	
Transfusion history				0.171
Yes, n (%)	26 (11.7)	36 (8.2)	52 (11.7)	
No, n (%)	157 (70.7)	341 (77.7)	342 (77.0)	
Unknown, n (%)	39 (17.6)	62 (14.1)	50 (11.3)	

a) Control group 1: patients with non-hematologic malignancy, SNUH, 1997–1998.
b) Control group 2: subjects with non-malignant conditions, SNUH, 1997–1998.
c) Pearson's χ^2 test.

Table II. Odds Ratios for the Association between Risk Factors and Non-Hodgkin's Lymphoma in Cases and Controls, Seoul National University Hospital, Korea, 1997–1998

Characteristics	Control 1		Control 2	
	Crude OR[a]	95%CI	Crude OR[b]	95%CI
Smoking				
Ever	0.78	0.55–1.11	0.67	0.47–0.95
Never	1.00		1.00	
Alcohol				
Ever	0.66	0.46–0.95	0.64	0.45–0.92
Never	1.00		1.00	
Transfusion				
≥1 pint	1.57	0.92–2.69	1.09	0.66–1.81
Never	1.00		1.00	
HBsAg				
Positive	1.84	1.07–3.14	2.91	1.61–5.25
Negative	1.00		1.00	
Anti-HCV Ab				
Positive	2.02	0.70–5.85	1.20	0.47–3.10
Negetive	1.00		1.00	

a) Risk of non-Hodgkin's lymphoma using control group 1 as a reference group.
b) Risk of non-Hodgkin's lymphoma using control group 2 as a reference group.

Table III. HBsAg-positive Rates and Odds Ratios for the Association between HBV Infection and Non-Hodgkin's Lymphoma According to Immunophenotypes

Immuno-phenotype	HBsAg (+) n (%)	Control 1		Control 2	
		Crude OR[a] (95%CI)	Adjusted OR[b] (95%CI)	Crude OR[c] (95%CI)	Adjusted OR[b] (95%CI)
Total (n=222)	28 (12.6)	1.84 (1.07–3.14)	1.99 (1.05–3.75)	2.91 (1.61–5.25)	3.85 (1.87–7.92)
B-Cell (n=136)	19 (14.0)	2.07 (1.13–3.78)	2.43 (1.17–5.01)	3.27 (1.70–6.29)	4.57 (2.03–10.29)
T-Cell (n=58)	4 (6.9)	0.94 (0.32–2.77)	0.55 (0.12–2.48)	1.49 (0.49–4.51)	0.96 (0.21–4.47)

a) Risk of specified immunopheotype of lymphoma among HBV carriers using control group 1 as a reference group.
b) Adjusted for age, sex, smoking, alcohol drinking, transfusion history, and anti-HCV antibody.
c) Risk of specified immunopheotype of lymphoma among HBV carriers using control group 2 as a reference group.

Table IV. HBsAg-positive Rate of B-Cell Non-Hodgkin's Lymphoma Patients and Controls, According to Age Groups, with Odds Ratios of B-Cell Non-Hodgkin's Lymphoma among HBsAg-positive Patients and Their 95% Confidence Intervals within Specified Age Groups

Age (yr.)	Cases		Control 1		Control 2		OR[a] (95%CI)
	n[b]	%	n[b]	%	n[b]	%	
≤29	4/17	23.5	2/53	3.8	5/60	8.3	4.66 (1.20–18.10)
30–49	7/37	18.9	11/140	7.9	9/138	6.5	3.01 (1.18–7.71)
≥50	8/82	9.8	19/246	7.7	7/246	2.8	1.94 (0.85–4.44)

a) Risks of B-cell non-Hodgkin's lymphoma among HBsAg-positive patients within specified age groups using both control groups 1 and 2 as reference groups.
b) Number of patients tested positive for HBsAg within the specified age group/total number of patients within the specified age group.

year-old or younger, 30–49, and 50-year-old or older age groups, respectively (Table IV).

Antibody to HBsAg (anti-HBsAb) was positive in 131 (59.0%) out of 222 patients with lymphoma, 287 (65.7%) out of 437 patients in control group 1, and 282 (63.5%) out of 444 subjects in control group 2. Anti-HCV antibody was detected in 7 (3.3%) out of 214 patients with lymphoma, 7 (1.6%) out of 426 patients in control group 1, and 12 (2.7%) out of 439 subjects in control group 2. No significant differences were found in the anti-HBsAb and anti-HCV antibody-positive rates for the three groups (*P*=0.15, *P*=0.65, respectively). Three patients were found to be positive for both HBsAg and anti-HCV antibody. None tested positive for anti-HIV antibody.

Data on the date of detection of HBV carrier status were available for ten out of 28 HBsAg-positive patients with non-Hodgkin's lymphoma. All ten of these patients were diagnosed as carriers prior to being diagnosed with non-Hodgkin's lymphoma and the mean interval between detection of carrier status and diagnosis of non-Hodgkin's lymphoma was 100 months (2 to 223 months).

DISCUSSION

The results of this case-control study suggest that HBsAg carrier status is associated with B-cell non-Hodgkin's lymphoma. Compared with HBsAg-negative subjects, the risk of developing B-cell non-Hodgkin's lymphoma was increased in HBsAg-positive carriers by two to threefold. This association was independent of age, sex, transfusion history, smoking, alcohol drinking and HCV infection.

A high prevalence of HBV infection among patients with non-Hodgkin's lymphoma has been reported by several investigators. Liang *et al.* reported a high positive rate of 22% for HBsAg in their study on 484 non-Hodgkin's lymphoma patients in Hong Kong.[9] The same authors also reported a high prevalence of 27% among 100 patients with non-Hodgkin's lymphoma in their prospective study.[10] Kumagai *et al.* and Markovic *et al.* reported the prevalence of HBsAg carriers to be 3.2% in Japan and Slovenia, which is lower than that of Hong Kong, but still higher than the general population in those countries.[11, 12]

The most recent studies performed in Romania and Japan also reported a strikingly higher prevalence of HBV and HCV infection among non-Hodgkin's lymphoma patients, 29.5% and 30.8%, and 6.9% and 8.1%, respectively.[13, 14] However, most of these studies were conducted without controls and the HBsAg-positive rate was compared to that of the general population.

Three likely explanations have been proposed for the association between HBV infection and non-Hodgkin's lymphoma. One hypothesis is that the risk of viral infection or reactivation increases due to the direct immunosuppressive effect of the lymphoma. The second hypothesis is that HBV carrier status itself might be responsible for lymphomagenesis. Based on the findings that HBV-specific nucleic acid sequences have been detected in peripheral blood mononuclear cells and in the hematopoietic tumor cells in HBsAg-positive patients,[18–20] it could be hypothesized that persistence of HBV in the peripheral blood mononuclear cells, like HCV, may result in chronic stimulation of B-cells which may lead to malignant B-cell lymphoma. The third hypothesis is that another unknown virus with a mode of transmission similar to HBV might be responsible for the lymphomagenesis. Viruses can contribute to the development of human tumors, as evidenced by Epstein-Barr virus and HTLV-1, which have been found to be associated with Burkitt's lymphoma and adult T cell leukemia-lymphoma.[21]

The results of our case-control study support the second or third hypothesis, namely, that viral infection, possibly by HBV, might play a pathogenic role in the development of malignant lymphoma. Of the 28 non-Hodgkin's lymphoma patients, at least ten patients were diagnosed as carriers prior to being diagnosed with non-Hodgkin's lymphoma with a mean duration of 100 months. These ten patients had been chronic carriers before the immunosuppressive effect of lymphoma could have influenced them. Although reactivation of hepatitis B has been reported in HBsAg-negative, anti-hepatitis B core antibody-positive patients receiving immunosuppressive therapy,[22, 23] no spontaneous reactivation has been reported in non-Hodgkin's lymphoma patients without concomitant immunosuppressive therapy. Our findings firmly oppose the first hypothesis. Moreover, our result that only B-cell and not T-cell non-Hodgkin's lymphoma is associated with HBV infection also support the second hypothesis. The fact that the risk of B-cell non-Hodgkin's lymphoma was higher in the younger age groups calls for special attention. We observed that the HBsAg-positive rate was highest in the youngest age group, then decreased linearly with aging in lymphoma patients in contrast to the control groups (Fig. 1). Liang *et al.* also observed that HBsAg-positive non-Hodgkin's lymphoma patients are younger than HBsAg-negative patients; the mean and median ages of the HBsAg-positive and -negative patients were 46.5 and 52.6

years, and 48 and 53 years, respectively.[9, 10] The natural decline of HBsAg-positive rate with aging and the shortened life expectancy of HBV carriers have been suggested as possible mechanisms,[9] but these cannot explain the similar HBsAg-positive rate across the age groups in controls.

In HBV endemic countries, most infection occurs during childhood by perinatal transmission and is followed by chronic carriage of HBV.[24] Perinatally acquired HBV undergoes an immune tolerance phase, which permits active viral replication without hepatitis for 2 to 3 decades, and then enters a virus clearance phase.[25] Younger age groups are more likely to be infected with actively replicating HBV represented by high HBV DNA titer and positive HBeAg (hepatitis B e antigen), which in turn, are more likely to stimulate B cell proliferation. Based on our results, we support the second hypothesis that actively replicating HBV may induce B-cell proliferation by chronic antigenic stimulation and play a pathogenic role in non-Hodgkin's lymphoma, especially in younger patients. The possibility of unidentified virus contributing to lymphomagenesis remains. There may be a viral infection which shares the same mode of infection as HBV which would have contributed to lymphomagenesis. Epstein-Barr virus (EBV) could be one candidate. Viral shedding of EBV in salivary gland excretions permits early infections, usually within the first year of life, in developing countries and EBV persists in the infected host throughout life.[21]

We performed immunohistochemical staining to detect HBsAg and HBcAg (hepatitis B core antigen) in the paraffin-embedded, formalin-fixed lymphoma tissues of 28 HBsAg-positive patients and 15 HBsAg-negative controls but failed to identify HBsAg in any of the lymphoma or
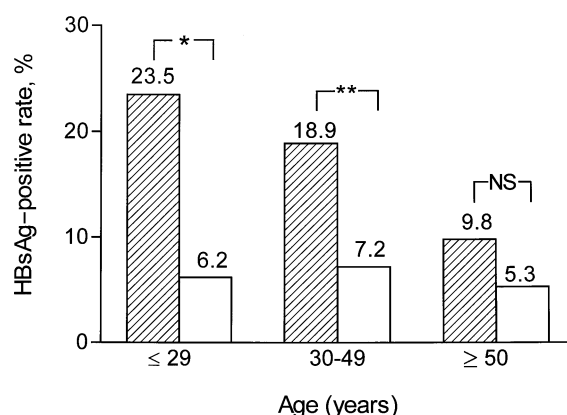

Fig. 1. HBsAg-positive rate in patients with B-cell non-Hodgkin's lymphoma versus controls, according to age groups. Striped bars represent HBsAg-positive rate in patients with B-cell non-Hodgkin's lymphoma; white bars represent HBsAg-positive rate in controls. * $P=0.038$. ** $P=0.026$.

control specimens. Although we failed to prove the etiologic role of HBV, this may also support our hypothesis that an etiologic role of HBV is confined to a relatively small proportion of lymphoma patients, and we believe that this aspect warrants further study.

Our study subjects showed no significant differences in anti-HCV antibody-positive rate. South Korea is endemic area for HBV infection, whereas the prevalence of HCV infection in the general population is, in terms of anti-HCV antibody positivity, 1.7%, which resembles that of developed countries. The prevalence of anti-HCV positivity remains below 1% till the 4th decade, then increases steadily with aging, up to 5.7% in the seventies. Chronic carriage of HCV and therefore chronic antigenic stimulation by HCV infection would be less likely, which would have contributed to the lack of association between HCV infection and non-Hodgkin's lymphoma in this study.

Several methodological limitations should be mentioned. The most serious disadvantage of a case-control study concerns the temporal ambiguity between exposure and the disease occurrence. Although we found a higher prevalence of HBV carriers among non-Hodgkin's lymphoma patients, it cannot be deduced whether this higher prevalence was a cause or an effect of lymphoma. Another limitation is the lack of information on other potential confounders. Most of the information was taken by reviewing medical records rather than by questionnaire or interview, resulting in many missing values. Thirdly, there may have been selection bias in choosing control groups. We used two control groups (hospital and community) in order to reduce the selection bias. The hospital controls would have similar risk of acquiring HBV infection to the case patients, owing to more frequent exposures to blood products and invasive procedures. We chose one homogenous group of gastric cancer patients as control group 1 to reduce other potential confounding variables, and because gastric cancer is the most common cancer in Korea. Given that the association was strongest in young patients, it may be possible that the choice of young controls was biased in some way. Due to differences in the age distribution of the lymphoma patients and control populations, young controls were mainly chosen from patients with sarcoma and fractures.

To our knowledge, this is the first case-control study on the association between HBV infection and non-Hodgkin's lymphoma, using two groups of age- and sex-matched controls. Our results suggest that chronic HBV infection might play a pathogenic role in lymphomagenesis in a certain subset of patients, especially in the younger age groups. Our findings warrant further investigation, including a prospective cohort study and molecular studies to examine the role of HBV in the pathogenesis of non-Hodgkin's lymphoma.

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