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Cohort study of non-Hodgkin lymphoma risk in association with hepatitis B virus infection in South Korea

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Abstract

Background—Hepatitis B virus (HBV) infection is common throughout Asia and Africa. Evidence is inconclusive regarding whether chronic HBV infection increases risk for non-Hodgkin lymphoma (NHL).

Methods—We conducted a cohort study of 603,585 South Korean workers and their dependents enrolled during 1992–1995. Serum hepatitis B surface antigen (HBsAg) measured at baseline indicated the presence of chronic HBV infection. We ascertained hematologic malignancies using national inpatient, outpatient, and mortality databases through 2006. Cox regression was used to evaluate associations with HBsAg status, adjusting for sex, age, and enrollment year.

Results—53,045 subjects (8.8%) were HBsAg positive at baseline. Subsequently, 133 HBsAg positive and 905 HBsAg negative individuals developed NHL. HBsAg positive subjects had elevated risk of NHL overall (incidence 19.4 vs. 12.3 per 100,000 person-years; adjusted hazard ratio [HR] 1.74, 95%CI 1.45–2.09). Among NHL subtypes, risk was significantly elevated in association with HBsAg positivity for diffuse large B cell lymphoma (N=325 cases; adjusted HR 2.01, 95%CI 1.48–2.75) and non-significantly elevated for follicular NHL (N=47; 1.67, 0.71–3.95) and T-cell NHL (N=75; 1.40, 0.67–2.92); risk was also elevated for other/unknown NHL subtypes (N=591; 1.65, 1.29–2.11). Elevated risk was also observed for malignant immunoproliferation (N=14; adjusted HR 3.79, 95%CI, 1.05–13.7), a category that includes Waldenström macroglobulinemia. Risk of these malignancies was consistently elevated in HBsAg positive subjects throughout 14 years of follow-up. HBsAg positivity was not associated with Hodgkin lymphoma, multiple myeloma, or various leukemias.

Interpretation—During extended follow-up, HBsAg positive individuals manifested an elevated risk of NHL, suggesting that chronic infection promotes lymphomagenesis.

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Conflicts of Interest

The authors do not have any conflicts of interest to disclose.

Author contributions

Eric A. Engels: Responsible for the study idea, conducted statistical analyses, wrote the manuscript.

Eo Rin Cho: Responsible for the data management, and conducted statistical analyses. Sun Ha Jee: Responsible for the study idea, conducted statistical analyses, and edited the manuscript.

Introduction

Hepatitis B virus (HBV) infects 350 million people worldwide and is responsible annually for 340,000 liver cancer cases and 500,000 to 1.2 million liver-related deaths (1,2). In endemic regions such as Asia and Africa, HBV infection commonly occurs in the perinatal period or during childhood (1). Infections acquired during early life often persist lifelong, in many cases leading to progressive liver disease (1).

Notably, a number of recent epidemiologic studies have suggested that chronic HBV infection may also increase the risk of non-Hodgkin lymphoma (NHL) (3–11). Such an association would parallel that between hepatitis C virus (HCV) and NHL, where more extensive evidence documents an etiologic relationship (10,12–16). The mechanism of lymphomagenesis for both viruses is postulated to involve chronic stimulation of B-cells in the setting of ongoing liver infection. However, most prior studies of HBV and NHL have been small retrospective case-control studies (N=200–600 cases total) and have relied upon convenience samples of controls that may not have been representative (3–9).

HBV infection was endemic in South Korea until 1995, when universal HBV vaccination of neonates was implemented (17). Prior to the introduction of vaccination, approximately 7% of South Korean adults had detectable plasma levels of hepatitis B surface antigen (HBsAg), consistent with chronic HBV infection (17). HBV infection remains common among South Korean adults, despite the availability of neonatal vaccination, due to infections acquired in childhood during prior years (18,19). Data from two hospital-based case-control studies in South Korea are among the studies supporting the possibility that chronic HBV infection increases NHL risk (3,4).

We have conducted a cohort study in South Korea to further evaluate the association between chronic HBV infection and the subsequent development of NHL. The present study included more than 600,000 subjects drawn from the general population, and follow-up information on the incidence of NHL was available during a 14-year period after measurement of HBV infection status. A further strength of the study is the availability of information on subtypes of NHL as well as on additional hematologic malignancy outcomes.

Methods

Cohort description and ascertainment of exposure and outcomes

The Korean Cancer Prevention Study (KCPS) is a cohort study of South Korean workers and their dependents (20). Eligible subjects were insured by the Korean Medical Insurance Corporation and participated in a biennial medical evaluation during 1992–1995 (baseline). Because the study involved routinely collected data, consent was not required. The study was approved by an institutional review board at Yonsei University (Seoul, South Korea) and the Johns Hopkins Bloomberg School of Public Health (Maryland, United States).

We excluded individuals who died before January 1, 1993 (n=904); who reported having cancer at or prior to the initial visit (n=3,811); who had missing information on weight, height, alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or alcohol use; extremely low body mass index (<16 kg/m^2), weight (≤30 kg), or height (≤1.30 m) (n=30,095), or evidence for infection with human immunodeficiency virus (HIV, n=425) or HCV (n=9708) based on national databases described below. After applying these exclusions, 1,284,586 people were potentially eligible. Finally, 603,585 of these individuals (47.0%) had baseline data on serum HBsAg status and were included as subjects in the present study.

At baseline, subjects completed a health questionnaire that included information on daily alcohol consumption. Routine measurement of liver function tests (ALT and AST) was also performed. HBsAg was measured in serum using a radioimmunoassay or reverse passive hemagglutination in participating laboratories. Because the great majority of HBV infections in South Korea originate in infancy or early childhood (17,21), we assumed that a single measurement indicating HBsAg positivity reflected chronic HBV infection of decades' duration. Nonetheless, a subset of subjects who enrolled in 1992 (mostly those who tested positive for HBsAg) had repeated measurement of HBsAg in 1994. Information was unavailable regarding markers of high-level HBV replication (e.g., serum HBV e antigen [HBeAg], HBV DNA) or repeated measurements of HBsAg for other subjects.

Subjects were followed from baseline until the earlier of December 31, 2006 or death as reported to the national statistical office. We used national databases with inpatient and outpatient diagnoses to ascertain the occurrence of hematologic malignancies. Inpatient data were complete for 1993–2006. Outpatient records were not available in 1992, incomplete during 1993–1996, and complete for 1997–2006. For deceased subjects, we also utilized information regarding the underlying cause of death (available 1992–2006). Based on International Classification of Diseases codes (version 10, http://apps.who.int/classifications/apps/icd/icd10online/), we evaluated the following outcomes: NHL overall (codes 82–85) and specifically follicular NHL (82), diffuse large B cell lymphoma (DLBCL, 83), T-cell NHL (84), and other/unknown NHL (85); malignant immunoproliferation (88); Hodgkin lymphoma (81); multiple myeloma (90); lymphoid leukemia (91); myeloid/monocytic leukemia (92–93); and other/unknown leukemia (94–95). Malignant immunoproliferation is defined to include Waldenström macroglobulinemia, heavy chain disease, and immunoproliferative small intestine disease.

National pharmacy insurance records available during 2001–2005 showed that only 4.2% of HBsAg positive people received HBV therapy with interferon α, lamivudine, or adefovir. Because these medication data were available for a limited time period, and because of the small number of treated people, we could not evaluate cancer risk in relation to HBV treatment.

Statistical analyses

For our primary analyses, we used diagnoses of hematologic malignancies that were present in inpatient, outpatient, or death records. There was generally good agreement between inpatient and outpatient records with respect to who was diagnosed with each malignancy (kappas 0.27–0.76, with most above 0.50), while the agreement of inpatient or outpatient records with death records was poorer (kappas 0.00–0.39, with most below 0.20). In a sensitivity analysis we evaluated only inpatient diagnoses, because outpatient diagnoses and diagnoses on mortality records were likely less accurate than inpatient diagnoses (e.g., due to incomplete ascertainment of outpatient diagnoses and difficulties in assigning causes of death). Among NHL subtypes, most were coded as "other/unknown NHL," while the most frequent specified subtype was DLBCL followed by T-cell NHL and follicular NHL. Some individuals had more than one NHL subtype diagnosed, but this occurred most commonly with respect to "other/unknown" NHLs.

We evaluated associations between the single measurement of baseline HBsAg status and subsequent risk of malignancies using Cox regression models. We report hazard ratios (HRs) and associated 95% confidence intervals (CIs) from both unadjusted models and models adjusted for sex, baseline age, and baseline calendar year. The proportional hazards assumption was assessed by incorporating an interaction between HBsAg status and follow-up time in the Cox model. We present life table estimates of the cumulative proportion of subjects who developed selected outcomes. In addition, to assess for possible confounding, we evaluated Cox models that included alcohol use or the presence of elevated ALT or AST results.

Because a minority of HBsAg positive people would not have had chronic infection (e.g., due to a laboratory error or resolution of acute infection), in another sensitivity analysis we compared NHL risk between two groups: 1) people with persistent HBsAg positivity in 1992 and 1994 (i.e., confirmed chronic infection), and 2) people who were HBsAg negative in 1992 and who were either not retested or who had another negative test in 1994 (uninfected). All statistical analyses were conducted using SAS (version 9.1, Cary, North Carolina).

Role of funding source

The study sponsors did not have any role in the design of the study; collection, analysis, and interpretation of the data; writing the report; or in the decision to submit the paper for publication. SHJ had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

The study included 603,585 people tested for HBsAg at health screening. Of these, 53,045 (8.8%) were HBsAg positive (Table 1). Compared with HBsAg negative subjects, HBsAg positive subjects were more likely to be male and were younger (median age 39 vs. 41 years). Most subjects were tested for HBsAg in 1992 or 1994, years when screening included mostly insured individuals rather than dependents. Alcohol use did not differ materially by HBsAg status. Hepatitis was more frequently present in HBsAg positive than HBsAg negative subjects, as manifested by abnormally elevated ALT and AST levels. Subjects were followed for a total of 8.0 million person-years (maximum 14 years).

Risks of various hematologic malignancies in HBsAg positive and HBsAg negative subjects are presented in Table 2. Among 1038 NHL cases, 12.8% were HBsAg positive at baseline, and HBsAg positivity was associated with an elevated risk of NHL (unadjusted HR 1.58, 95% CI 1.32–1.90). An elevated risk was significant only for the two most common NHL subtypes, DLBCL (HR 1.82, 95%CI 1.34–2.48) and other/unknown NHL (1.49, 95%CI 1.17–1.91), although there were nonsignificant increases for follicular and T-cell NHLs. Based on only 14 cases, risk of malignant immunoproliferation appeared elevated in HBsAg positive subjects, but this association was not significant (HR 2.91, 95%CI 0.81–10.4). HBsAg positivity was not associated with elevated risk of Hodgkin lymphoma, multiple myeloma, or the various leukemias (Table 2).

Notably, associations with HBsAg became stronger with adjustment for sex, age, and calendar year of testing (Table 2). Specifically, HBsAg positivity was associated with significantly increased risk of NHL overall (adjusted HR 1.74, 95%CI 1.45–2.09), DLBCL (2.01, 95%CI 1.48–2.75), and other/unknown NHL (1.65, 95%CI 1.29–2.11). After adjustment, the association with malignant immuoproliferation also became significant (adjusted HR3.79, 95% CI 1.05–13.7). Results for NHL appeared stronger in a sensitivity analysis in which we considered only outcomes recorded in inpatient records (Table 2).

Risk of selected hematologic malignancies is presented graphically in Figure 1. Risks of NHL (overall and for DLBCL and other/unknown NHL) and malignant immunoproliferation were higher in HBsAg positive subjects than in HBsAg negative subjects throughout the 14-year period of follow-up. Specifically, a small difference in the proportion of subjects with each outcome was apparent in the first few years after HBsAg testing, and this difference increased steadily over time. Likewise, the proportional hazards assumption was met for each outcome in Table 2, indicating that the effect of HBsAg positivity on risk of hematologic malignancy did not vary during follow-up (data not shown).

Adjustment for alcohol use did not affect the associations with HBsAg positivity (data not shown). Table 3 presents associations between the presence of abnormal liver function tests and risk of various hematologic malignancies. Subjects with an elevated AST had an increased risk of NHL overall. Elevated risks of multiple myeloma, lymphoid leukemia, and myeloid/monocytic leukemia were also observed in association with AST elevation. However, these associations were attenuated when we adjusted for HBsAg status and demographic characteristics (Table 3). Furthermore, the associations with multiple myeloma and leukemias were weaker for ALT (Table 3). Of note, in the multivariate models that included liver function test results and HBsAg status, HBsAg positivity remained a significant predictor of increased NHL risk, while the associations with ALT and AST became attenuated (Table 3). Finally, in a separate analysis restricted to HBsAg positive individuals, NHL risk did not differ between those with elevated liver function tests and those with normal liver function tests (data not shown).

Among 46,015 people who were HBsAg positive in 1992, a total of 41,311 had another test in 1994, of whom 36,502 (88.4%) were HBsAg positive again (i.e., confirmed chronic infection) and the remainder were HBsAg negative. In comparison, of the 446,841 people who were HBsAg negative in 1992, a total of 446,701 were either not retested in 1994 or were HBsAg negative again. In a sensitivity analysis in which we compared these two groups (i.e., confirmed chronic infection vs. the group without evidence of infection at either time point), associations with hematologic outcomes appeared similar to or slightly stronger than in the primary analyses. In particular, people with confirmed chronic HBV infection had an elevated risk for NHL overall (adjusted HR 2.00 (95%CI 1.63–2.46), DLBCL (2.27, 1.60–3.22), and malignant immunoproliferation (3.88, 0.83–18.0). No new associations with additional hematologic malignancies were identified.

Discussion

In this large cohort study of healthy workers and their families in South Korea, we documented an excess risk of NHL among people infected with HBV (adjusted HR 1.74, 95%CI 1.45–2.09). A strength of our study is that HBV infection was documented prospectively, and we demonstrated that the increased risk of NHL persisted during follow-up throughout a 14-year period. Furthermore, NHL risk remained elevated after we adjusted for potential confounding factors including demographic characteristics, alcohol use, and liver function test abnormalities. We did not see associations between HBsAg status and risk of Hodgkin lymphoma, multiple myeloma, or leukemia, suggesting that HBV does not contribute to the development of these hematologic malignancies and lending specificity to the association with NHL.

Prior studies of the relationship between HBV and NHL risk have been conducted in both HBV endemic countries (e.g., South Korea, China) and non-endemic countries (e.g., U.S., Australia) (3–11). As discussed in a recent systematic review (22), previous retrospective case-control studies have generally supported an association (odds ratios 1.5–3.6) (3–9). However, these studies have typically been somewhat small (N=200–600 cases) and have used unrepresentative convenience samples of controls (e.g., hospitalized patients with cancer, blood donors). In comparison, larger registry-based studies have provided mixed results. A population-based case-control study of elderly adults in the U.S. (N=33,940 NHL cases) failed to document associations between HBV infection and various specified NHL subtypes (10), but HBV prevalence was very low (0.2%) and may have been under-ascertained. Two prior cohort studies of HBV infected persons, similar in design to our study but smaller, have also been published. Ulcickas Yood et al. observed an elevated risk of NHL in a cohort of 3888 HBV infected patients in a U.S. health maintenance organization (hazard ratio 2.30 based on

8 NHL cases) (11). In contrast, Amin and coworkers found no elevation in NHL risk among 39,109 Australians reported to an HBV infection registry (23).

The collected evidence from these studies, along with data from our study demonstrating the presence of HBV infection more than a decade before NHL diagnosis, suggest that HBV may play a causal role in the development of NHL. If HBV infection causes NHL, the mechanism is unknown. One plausible mechanism could be that HBV-related hepatitis might cause chronic activation of B-cells, predisposing to DNA damage and transformation into lymphoma. Similar pathways are proposed for HCV-mediated lymphomagenesis (12,13,16). HBV DNA has been detected within peripheral blood B-cells (24), but it is uncertain whether HBV could directly transform lymphocytes, because based on limited data (4,5), HBV is not present in NHL tumor cells. In our study, NHL risk was increased among subjects with elevated ALT or AST, but the associations with HBsAg were not explained by these elevations, since we observed an independent effect of HBsAg positivity in multivariate models. Furthermore, we did not observe an additive risk for NHL among HBsAg positive people with elevated liver function tests. Likewise, Wang et al. did not find an elevated prevalence of serum HBeAg (a marker of high-level HBV replication and liver damage) among NHL cases (6).

Because various NHL subtypes likely have differing etiology (25), a strength of our study was the availability of subtype data for a large fraction of NHL cases. We found that HBsAg positive individuals had an elevated risk of DLBCL, the most common NHL subtype, which mirrors an association demonstrated for HCV (10,14,15). We also saw suggestive, although non-significant, associations with follicular and T-cell NHLs. Nonetheless, the associations that we observed with specific NHL subtypes should be interpreted cautiously, because over half of NHLs were coded as “other/unknown” subtype, and some people had more than one NHL subtype indicated (although in most instances, this occurred when there was both a specified subtype and “other/unknown” subtype). We found HBsAg positivity to be associated with a significantly elevated risk for other/unknown NHLs, and it is possible that this association is due to a large fraction of undiagnosed DLBCLs in this group. The group of other/unknown NHLs may also include cases of marginal zone and lymphoplasmacytic NHLs, low-grade NHL subtypes that have been associated with HCV (10,14,15,26). Of interest, a recent case report described an HBV-infected patient with splenic marginal zone NHL who developed a complete hematologic remission following a flare of her infection (27), suggesting that the tumor was linked immunologically with the infection.

Based on a small number of cases, we observed a borderline increased risk for malignant immunoproliferation in association with HBsAg positivity. This finding is notable because this poorly specified category of neoplasms includes Waldenström macroglobulinemia, which is essentially synonymous with lymphoplasmacytic lymphoma. Waldenström macroglobulinemia and lymphoplasmacytic lymphoma have also been linked with HCV infection (26). We are not aware of prior reports describing an elevated risk of immunoproliferative conditions among HBV infected people, although HBV is associated with the occurrence of other immune-related conditions including polyarteritis nodosa, glomerulonephritis, and potentially essential mixed cryoglobulinemia (28).

Strengths and limitations of our study should be considered. Strengths include the large size of the KCPS cohort, its representativeness of a healthy segment of the South Korean population, and the prospective documentation of HBsAg results. Although HBsAg was measured at only a single timepoint for most subjects, South Korea exhibits an endemic pattern of HBV infection, and most HBsAg positive individuals likely had chronic infection that had been present since childhood and that persisted throughout our follow-up (17,21). Indeed, for a sizeable subset of subjects, we were able to confirm that HBsAg positivity was chronic, and we showed that this group had similarly elevated risk (or perhaps even higher risk) for NHL and malignant

immunoproliferation. Unfortunately, we could not include additional serum markers (e.g., HBeAg, HBV DNA) that would reflect severity of HBV infection. Our results are unlikely to be due to confounding by infection with HCV or HIV, because these infections are rare in South Korea, and we excluded people with evidence for these infections from our study sample. We used several systems of records to ascertain the occurrence of hematologic malignancy, and we had sufficient data on subtypes of NHL to examine them separately. However, we could not retrieve medical records to obtain additional information or confirm the NHL subtype diagnoses.

In a country such as South Korea where HBV prevalence is high, a substantial number of cancer patients are at risk of developing severe HBV-related liver disease with initiation of chemotherapy, and this risk may be reduced with use of appropriate chemoprophylaxis with lamivudine (29). In addition to the 12.8% of South Korean NHL cases who were HBsAg positive, a large fraction of NHL patients would be expected to have serologic evidence for resolved HBV infection (i.e., absence of HBsAg with antibody to HBV core antigen), although we did not have data on this group. Recent evidence points to a high risk of HBV reactivation among such patients in association with use of rituximab-containing chemotherapy regimens (30,31). Finally, even though we did not see an increased prevalence of HBsAg in association with other hematologic malignancies, HBsAg prevalence was nonetheless as high as in the Korean general population (~9%). HBsAg positive patients with these other malignancies would also be at high risk for HBV-related liver disease induced by cytotoxic chemotherapy. These considerations support systematic screening for HBV infection among patients with hematologic malignancy who live in endemic regions or have emigrated from these regions, and appropriate monitoring and prophylaxis of HBV infected patients to mitigate HBV-induced liver disease arising during chemotherapy (32).

Additional research is required to clarify whether the association between HBV infection and NHL is causal. Even if the association proves causal, given the modest magnitude of the association between HBsAg positivity and NHL risk, HBV infection would account for only a small minority of NHL cases in endemic regions (e.g., population attributable risk = 6% in our Korean cohort) (33). Thus, while universal HBV vaccination is effective in preventing HBV infection and dramatically reduces the occurrence of liver cancer in endemic regions (34), vaccination programs would be expected to have a limited effect on NHL incidence. Nonetheless, among HBV infected people who develop NHL, it is possible that HBV explains a sizeable fraction of cases (e.g., attributable risk = 43% in our cohort) (33). For HCV-infected patients with low-grade NHL (especially marginal zone lymphomas), HCV treatment appears effective in leading to hematologic remission (35). Thus, we speculate that therapy directed at HBV in similar low-grade NHLs might similarly lead to a clinical response and obviate the need for chemotherapy. It will be important to evaluate this possibility in appropriate clinical series.

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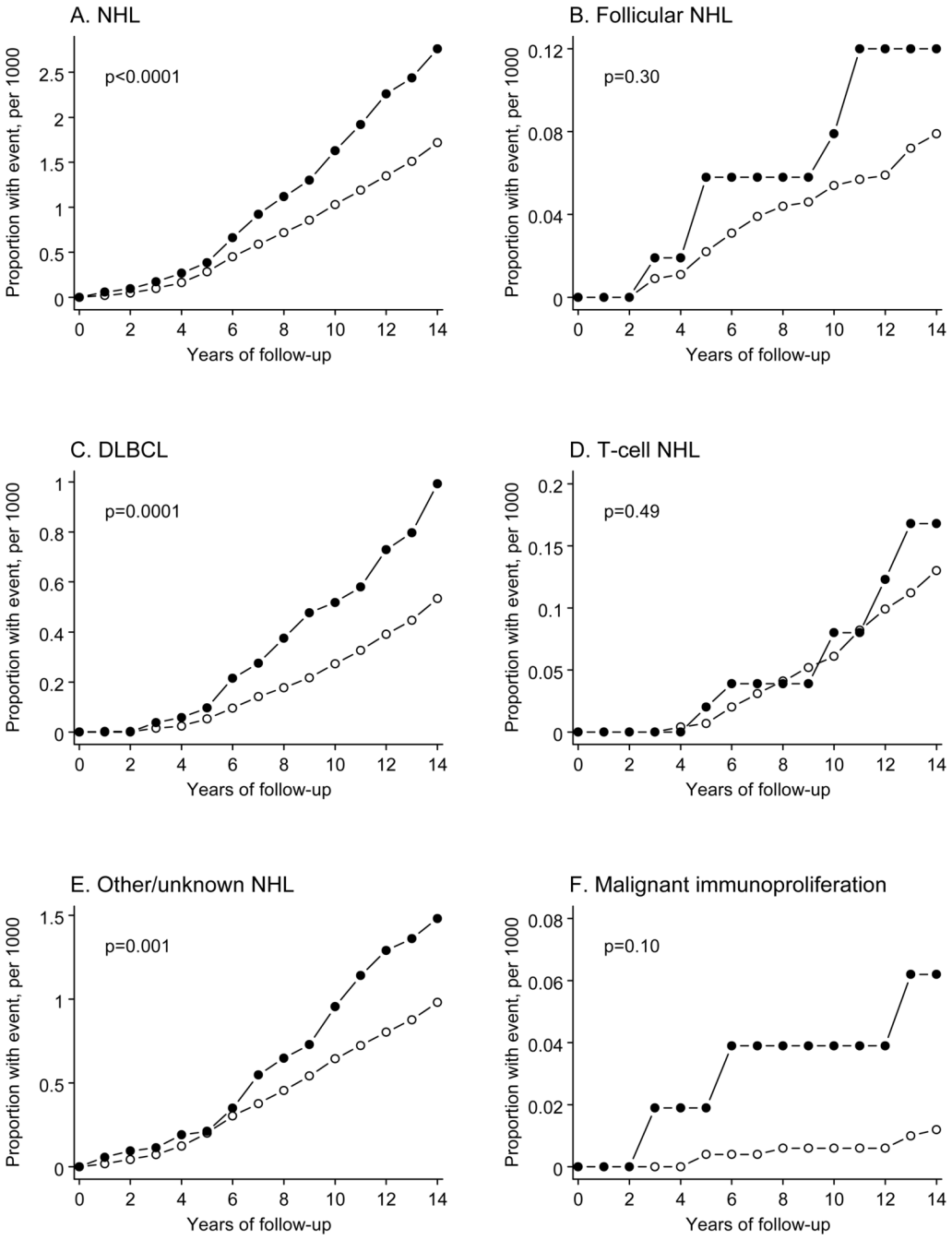

Figure 1.

Cumulative incidence of hematologic malignancies among HBV infected and uninfected people in South Korea. Results are shown for NHL overall, four subtypes of NHL, and malignant immunoproliferation. Estimates were derived using life table methods. The filled circles represent data for HBV infected people, and the open circles represent data for uninfected people. The vertical scale varies across the panels. P-values are from the unadjusted Cox models presented in Table 2.

Table 1

Characteristics of HBsAg positive and HBsAg negative subjects in the Korean Cancer Prevention Study cohort (N=603,585)

Characteristic	HBsAg+ (N=53,045)	HBsAg− (N=550,540)
Sex, n (%)		
Male	44,801 (84.5)	430,766 (78.2)
Female	8,244 (15.5)	119,774 (21.8)
Age in years at testing, n (%)		
30–39	26,567 (50.1)	245,172 (44.5)
40–49	17,478 (33.0)	186,463 (33.9)
50–59	8307 (15.7)	106,245 (19.3)
60+	693 (1.3)	12,660 (2.3)
Median age	39	41
Calendar year at testing, n (%)		
1992	46,015 (86.8)	446,841 (81.2)
1993	1269 (2.4)	27,349 (5.0)
1994	4962 (9.4)	61,242 (11.1)
1995	799 (1.5)	15,108 (2.7)
Alcohol use in grams/day, n (%)		
0	18,983 (35.8)	191,731 (34.8)
1–24.9	24,998 (47.1)	263,418 (47.9)
25–49.9	5314 (10.0)	56,196 (10.2)
50–99.9	2833 (5.3)	29,209 (5.3)
100+	917 (1.7)	9,986 (1.8)
ALT, n (%)		
Normal	40,394 (76.2)	495,880 (90.1)
Abnormal	12,651 (23.9)	54,660 (9.9)
AST, n (%)		
Normal	42,788 (80.7)	512,626 (93.1)
Abnormal	10,257 (19.3)	37,914 (6.9)

Abbreviations: HBsAg hepatitis B surface antigen, ALT alanine aminotransferase, AST aspartate aminotransferase

Table 2

Incidence of hematologic malignancies according to hepatitis B infection status.

Outcome	Number of events		Incidence, per 100,000 person-years		Unadjusted HR (95%CI) p-value	Adjusted HR (95%CI)* p-value
	HBsAg+	HBsAg−	HBsAg+	HBsAg−		
All outcomes						
NHL	133	905	19.4	12.3	1.58 (1.32–1.90) <0.0001	1.74 (1.45–2.09) <0.0001
Follicular NHL	6	41	0.88	0.56	1.57 (0.67–3.70) 0.30	1.67 (0.71–3.95) 0.24
DLBCL	47	278	6.86	3.79	1.82 (1.34–2.48) 0.0001	2.01 (1.48–2.75) <0.0001
T-cell NHL	8	67	1.17	0.91	1.29 (0.62–2.69) 0.49	1.40 (0.67–2.92) 0.37
Other/unknown NHL	72	519	10.5	7.07	1.49 (1.17–1.91) 0.001	1.65 (1.29–2.11) <0.0001
Malignant immunoproliferation	3	11	0.44	0.15	2.91 (0.81–10.4) 0.10	3.79 (1.05–13.7) 0.04
Hodgkin lymphoma	8	97	1.17	1.32	0.88 (0.43–1.82) 0.73	0.99 (0.48–2.04) 0.98
Multiple myeloma	19	273	2.77	3.72	0.74 (0.47–1.19) 0.21	0.90 (0.56–1.43) 0.64
Lymphoid leukemia	12	148	1.75	2.02	0.87 (0.48–1.17) 0.64	0.96 (0.53–1.74) 0.90
Myeloid/monocytic leukemia	42	407	6.13	5.55	1.11 (0.81–1.52) 0.52	1.21 (0.88–1.66) 0.25
Other/unknown leukemia	20	190	2.92	2.59	1.13 (0.71–1.79) 0.60	1.24 (0.78–1.97) 0.36
Inpatient outcomes only						
NHL	90	537	13.1	7.32	1.81 (1.44–2.26) <0.0001	2.02 (1.61–2.53) <0.0001
Follicular NHL	3	16	0.44	0.22	2.02 (0.59–6.94) 0.26	2.18 (0.63–7.54) 0.22
DLBCL	38	196	5.55	2.67	2.09 (1.48–2.96) <0.0001	2.36 (1.67–3.35) <0.0001
T-cell NHL	7	34	1.02	0.46	2.23 (0.99–5.03) 0.05	2.30 (1.02–5.21) 0.05
Other/unknown NHL	42	291	6.13	3.97	1.56 (1.13–2.15) 0.007	1.74 (1.26–2.41) 0.0008

Outcome	Number of events		Incidence, per 100,000 person-years		Unadjusted HR (95%CI)	Adjusted HR (95%CI)*
	HBsAg+	HBsAg−	HBsAg+	HBsAg−	p-value	p-value
Malignant immunoproliferation	1	6	0.15	0.08	1.78 (0.21–14.8) 0.59	2.32 (0.28–19.5) 0.44
Hodgkin lymphoma	3	46	0.44	0.63	0.70 (0.22–2.25) 0.55	0.75 (0.23–2.42) 0.63
Multiple myeloma	14	189	2.04	2.58	0.79 (0.46–1.36) 0.40	0.94 (0.55–1.63) 0.83
Lymphoid leukemia	4	68	0.58	0.93	0.63 (0.23–1.73) 0.37	0.70 (0.26–1.93) 0.50
Myeloid/monocytic leukemia	23	270	3.36	3.68	0.88 (0.57–1.34) 0.54	0.92 (0.60–1.41) 0.71
Other/unknown leukemia	6	47	0.88	0.64	1.31 (0.56–3.06) 0.54	1.50 (0.64–3.51) 0.36

Abbreviations: HBsAg hepatitis B surface antigen, HR hazard ratio, CI confidence interval, NHL non-Hodgkin lymphoma, DLBCL diffuse large B cell lymphoma
Statistically significant results are underlined.

*Adjusted hazard ratios are adjusted for sex, age at baseline, and calendar year at baseline.

Table 3

Associations of abnormal liver function tests and hepatitis B infection with risk of hematologic malignancies.

Outcome	Univariate model	Multivariate model*	
	Abnormal LFT HR (95%CI) p-value	Abnormal LFT HR (95%CI) p-value	HBsAg+ HR (95%CI) p-value
ALT results			
NHL	1.29 (1.08–1.54) 0.005	1.22 (1.02–1.46) 0.03	1.70 (1.41–2.04) <0.0001
Follicular NHL	1.69 (0.79–3.62) 0.18	1.68 (0.77–3.66) 0.19	1.55 (0.65–3.71) 0.32
DLBCL	1.20 (0.86–1.66) 0.28	1.10 (0.79–1.53) 0.58	1.99 (1.46–2.72) <0.0001
T-cell NHL	0.47 (0.17–1.28) 0.14	0.45 (0.16–1.24) 0.12	1.50 (0.72–3.13) 0.28
Other/unknown NHL	1.43 (1.14–1.79) 0.002	1.36 (1.08–1.72) 0.009	1.58 (1.23–2.03) 0.0003
Malignant immunoproliferation	0.63 (0.08–4.84) 0.66	0.68 (0.09–5.34) 0.71	3.91 (1.08–14.2) 0.04
Hodgkin lymphoma	1.16 (0.65–2.08) 0.61	1.19 (0.66–2.15) 0.56	0.97 (0.47–2.00) 0.93
Multiple myeloma	1.02 (0.70–1.47) 0.94	1.05 (0.73–1.53) 0.78	0.89 (0.56–1.42) 0.63
Lymphoid leukemia	1.53 (1.00–2.35) 0.05	1.58 (1.02–2.43) 0.04	0.91 (0.50–1.64) 0.75
Myeloid/monocytic leukemia	1.15 (0.87–1.53) 0.33	1.15 (0.86–1.53) 0.34	1.19 (0.86–1.64) 0.30
Other/unknown leukemia	1.16 (0.77–1.75) 0.47	1.14 (0.75–1.73) 0.54	1.22 (0.77–1.94) 0.40
AST results			
NHL	1.35 (1.10–1.66) 0.004	1.16 (0.94–1.42) 0.17	1.71 (1.42–2.06) <0.0001
Follicular NHL	1.80 (0.77–4.24) 0.18	1.70 (0.71–4.08) 0.23	1.56 (0.65–3.73) 0.32
DLBCL	1.36 (0.95–1.96) 0.10	1.13 (0.78–1.64) 0.51	1.99 (1.45–2.72) <0.0001
T-cell NHL	1.09 (0.47–2.51) 0.84	0.99 (0.42–2.29) 0.97	1.40 (0.67–2.93) 0.37
Other/unknown NHL	1.35 (1.03–1.77) 0.03	1.16 (0.88–1.52) 0.30	1.62 (1.26–2.08) 0.0002
Malignant immunoproliferation	2.08 (0.47–9.27) 0.34	1.85 (0.40–8.54) 0.43	3.55 (0.97–13.0) 0.06
Hodgkin lymphoma	0.88 (0.41–1.90) 0.75	0.82 (0.38–1.77) 0.61	1.01 (0.49–2.08) 0.98
Multiple myeloma	1.54 (1.07–2.22) 0.02	1.40 (0.97–2.03) 0.08	0.86 (0.54–1.38) 0.54
Lymphoid leukemia	2.21 (1.43–3.41) 0.0003	2.09 (1.35–3.25) 0.001	0.88 (0.48–1.59) 0.66
Myeloid/monocytic leukemia	1.44 (1.07–1.95) 0.02	1.32 (0.97–1.79) 0.08	1.17 (0.85–1.61) 0.34
Other/unknown leukemia	1.30 (0.82–2.05) 0.27	1.14 (0.72–1.82) 0.57	1.22 (0.77–1.94) 0.40

Abbreviations: LFT liver function test, HBsAg hepatitis B surface antigen, HR hazard ratio, CI confidence interval, ALT alanine aminotransferase, AST aspartate aminotransferase, NHL non-Hodgkin lymphoma, DLBCL diffuse large B cell lymphoma
Statistically significant results are underlined.

* The multivariate model includes the specified liver function test abnormality, HBsAg positivity, and adjustment for sex, age at baseline, and calendar year at baseline.