Hepatitis B virus infection and risk of non-Hodgkin lymphoma in South Korea: a cohort study

Eric A Engels, Eo Rin Cho, Sun Ha Jee

Summary

Background Hepatitis B virus (HBV) infection is common throughout Asia and Africa. Whether chronic HBV infection increases risk of non-Hodgkin lymphoma (NHL) is unclear. We aimed to assess the association between chronic HBV infection and subsequent development of NHL in a South Korean cohort.

Methods The Korean Cancer Prevention Study is a cohort study of South Korean workers and their dependants enrolled during 1992–95. From this cohort, we excluded individuals who died before Jan 1, 1993, who had cancer at or before the initial visit, who had missing information about weight, height, alanine aminotransferase or aspartate aminotransferase concentrations, or alcohol use, or who had evidence of HIV or HCV infection. Of 1 284 586 eligible participants, 603 585 had baseline data for serum hepatitis B surface antigen (HBsAg) status and were included in our study. We regarded HBsAg positivity at baseline as evidence of chronic HBV infection. Participants were followed up from baseline until Dec 31, 2006. We used national databases of inpatient and outpatient diagnoses and mortality records to ascertain occurrence of haematological malignancies. We assessed incidence of NHL overall and of NHL subtypes, malignant immunoproliferation, Hodgkin's lymphoma, multiple myeloma, and various leukaemias. We used Cox regression to evaluate associations with HBsAg status, adjusting for sex, age, and enrolment year.

Findings 53 045 (9%) of 603 585 participants tested positive for HBsAg at baseline. Subsequently, 133 HBsAg-positive and 905 HBsAg-negative individuals developed NHL. HBsAg-positive participants had an increased risk of NHL overall compared with those who were HBsAg-negative (incidence 19·4 *vs* 12·3 per 100 000 person-years; hazard ratio [HR] 1·74, 95% CI 1·45–2·09, adjusted for sex, age at baseline, and enrolment year). Among NHL subtypes, HBsAg positivity was associated with increased risk of diffuse large B-cell lymphoma (n=325, incidence 6·86 *vs* 3·79 per 100 000 person-years; adjusted HR 2·01, 1·48–2·75) and other or unknown subtypes (n=591, incidence 10·5 *vs* 7·07 per 100 000 person-years; adjusted HR 1·65, 1·29–2·11), compared with HBsAg negativity. Increased risk was also recorded for malignant immunoproliferation (n=14, incidence 0·44 *vs* 0·15 per 100 000 person-years; adjusted HR 3·79, 1·05–13·7). Risk of these malignancies was consistently raised in HBsAg-positive participants throughout 14 years of follow-up. HBsAg positivity was not associated with follicular or T-cell NHL, Hodgkin's lymphoma, multiple myeloma, or various leukaemias.

Interpretation During extended follow-up, HBsAg-positive individuals had an increased risk of NHL, suggesting that chronic HBV infection promotes lymphomagenesis.

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Introduction

350 million people worldwide are infected with hepatitis B virus (HBV), and the virus causes 340 000 cases of liver cancer and 500 000 to 1·2 million liver-related deaths per year.[1,2] In endemic regions such as Asia and Africa, infection often occurs perinatally or during childhood.[1] Infections acquired during early life often persist for life, in many cases leading to progressive liver disease.[1] Notably, results of several epidemiological studies have suggested that chronic infection might also increase risk of non-Hodgkin lymphoma (NHL).[3–11] Such an association would parallel that between hepatitis C virus and NHL, for which extensive evidence shows a causal relation.[10,12–16] The mechanism of lymphomagenesis for both viruses is postulated to involve chronic stimulation of B cells in the setting of sustained liver infection. However, most previous studies of HBV and NHL have been small retrospective case-control studies (200–600 cases in total) and have relied on convenience samples of controls that might not have been representative.[3–9]

HBV infection was endemic in South Korea until 1995, when universal HBV vaccination of neonates was implemented.[17] Before the introduction of vaccination, about 7% of South Korean adults had detectable plasma concentrations of hepatitis B surface antigen (HBsAg), which is consistent with chronic HBV infection.[17] HBV infection remains common in South Korean adults, despite the availability of neonatal vaccination, because of infections acquired in childhood during previous 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 undertook a cohort study in South Korea with the aim of further assessing the association

between chronic HBV infection and the subsequent development of NHL.

Methods

Participants

The Korean Cancer Prevention Study (KCPS) is a cohort study of South Korean workers and their dependants.[20] Eligible participants were insured by the Korean Medical Insurance Corporation and underwent a biennial medical assessment during 1992–95 (baseline). Since the study used routinely obtained data, consent was not required. The study was approved by institutional review boards at Yonsei University (Seoul, South Korea) and the Johns Hopkins Bloomberg School of Public Health (MD, USA).

From the KCPS cohort, we excluded individuals who died before Jan 1, 1993 (n=904); who reported having cancer at or before the initial visit (n=3811); who had missing information about weight, height, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) concentrations, or alcohol use; very low body-mass index (<16 kg/m²), weight (≤30 kg), or height (≤1·30 m) (n=30 095); or evidence of infection with HIV (n=425) or HCV (n=9708) on the basis of national databases. After application of these criteria, 1284 586 people were potentially eligible. 603 585 (47%) of these individuals had baseline data for serum HBsAg status and were included as participants in our study.

	HBsAg-positive participants (N=53 045)	HBsAg-negative participants (N=550 540)
Sex		
Male	44 801 (84%)	430 766 (78%)
Female	8244 (16%)	119 774 (22%)
Age at testing (years)		
30–39	26 567 (50%)	245 172 (45%)
40–49	17 478 (33%)	186 463 (34%)
50–59	8307 (16%)	106 245 (19%)
≥60	693 (1%)	12 660 (2%)
Median	39 (34–46)	41 (35–48)
Calendar year at testing		
1992	46 015 (87%)	446 841 (81%)
1993	1269 (2%)	27 349 (5%)
1994	4962 (9%)	61 242 (11%)
1995	799 (2%)	15 108 (3%)
Alcohol use (g per day)		
0	18 983 (36%)	191 731 (35%)
1·0–24·9	24 998 (47%)	263 418 (48%)
25·0–49·9	5314 (10%)	56 196 (10%)
50·0–99·9	2833 (5%)	29 209 (5%)
≥100	917 (2%)	9986 (2%)
ALT concentration		
Normal	40 394 (76%)	495 880 (90%)
Abnormal	12 651 (24%)	54 660 (10%)
AST concentration		
Normal	42 788 (81%)	512 626 (93%)
Abnormal	10 257 (19%)	37 914 (7%)

Data are number (%) or median (IQR). HBsAg=hepatitis B surface antigen. ALT=alanine aminotransferase. AST=aspartate aminotransferase.

Table 1: **Baseline characteristics, by HBsAg status**

For **International Classification of Diseases codes** see http://apps.who.int/classifications/apps/icd/icd10online/

Procedures

At baseline, participants completed a health questionnaire that included information about daily alcohol consumption. Routine measurement of liver function (ALT and AST concentrations) was also done. HBsAg was measured in serum with radioimmunoassay or reverse passive haemagglutination in participating laboratories. Because many HBV infections in South Korea originate in infancy or early childhood,[17,21] we assumed that one measurement indicating HBsAg positivity showed a chronic infection of decades' duration. Nonetheless, a subset of participants enrolled in 1992 (mostly those who tested positive for HBsAg) had repeated measurement of HBsAg in 1994. Information was unavailable about markers of high-level HBV replication (eg, serum HBV e antigen [HBeAg], HBV DNA) or repeated measurements of HBsAg for other participants.

Participants were followed up from baseline until death, as reported to the national statistical office, or Dec 31, 2006. We used national databases with inpatient and outpatient diagnoses to ascertain the occurrence of haematological malignancies. Inpatient data were complete for 1993–2006. Outpatient records were not available for 1992, incomplete during 1993–96, and complete for 1997–2006. For deceased participants, we also used information regarding the underlying cause of death (available for 1992–2006). On the basis of International Classification of Diseases codes (version 10), we assessed several outcomes: NHL overall (codes 82–85) and specifically follicular NHL (82), diffuse large B-cell lymphoma (DLBCL; 83), T-cell NHL (84), and other or unknown NHL (85); malignant immunoproliferation (88); Hodgkin's lymphoma (81); multiple myeloma (90); lymphoid leukaemia (91); myeloid or monocytic leukaemia (92–93); and other or unknown leukaemia (94–95). Malignant immunoproliferation includes Waldenström macroglobulinaemia, heavy-chain disease, and immunoproliferative small-intestine disease.

National pharmacy insurance records available for 2001–05 showed that only 4·2% of people who were positive for HBsAg received HBV treatment with interferon alfa, lamivudine, or adefovir. Because these data were not available throughout follow-up, and because of the small number of treated people, we could not assess cancer risk in relation to HBV treatment.

Statistical analysis

For our primary analyses, we used diagnoses of malignant haematological disease that were present in inpatient, outpatient, or death records. There was generally good agreement between inpatient and

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	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's 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 leukaemia	12	148	1·75	2·02	0·87 (0·48–1·17; 0·64)	0·96 (0·53–1·74; 0·90)
Myeloid/monocytic leukaemia	42	407	6·13	5·55	1·11 (0·81–1·52; 0·52)	1·21 (0·88–1·66; 0·25)
Other/unknown leukaemia	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)
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's 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 leukaemia	4	68	0·58	0·93	0·63 (0·23–1·73; 0·37)	0·70 (0·26–1·93; 0·50)
Myeloid/monocytic leukaemia	23	270	3·36	3·68	0·88 (0·57–1·34; 0·54)	0·92 (0·60–1·41; 0·71)
Other/unknown leukaemia	6	47	0·88	0·64	1·31 (0·56–3·06; 0·54)	1·50 (0·64–3·51; 0·36)

HBsAg=hepatitis B surface antigen. +=positive. –=negative. HR=hazard ratio. NHL=non-Hodgkin lymphoma. DLBCL=diffuse large B-cell lymphoma. *Adjusted hazard ratios are adjusted for sex, age at baseline, and calendar year at baseline.

Table 2: **Incidence of haematological malignancies, by HBsAg status**

outpatient records with respect to who was diagnosed with each malignancy (κ 0·27–0·76, with most higher than 0·50), but the agreement of inpatient or outpatient records with death records was poorer (κ 0·00–0·39, with most lower than 0·20). In a sensitivity analysis, we assessed only inpatient diagnoses, because outpatient diagnoses and diagnoses on mortality records were likely to be less accurate than inpatient diagnoses (eg, because of incomplete ascertainment of outpatient diagnoses and difficulties in assignment of causes of death). Among NHL subtypes, most were coded as other or unknown NHL, and the most frequent specified subtype was DLBCL followed by T-cell NHL and follicular NHL. Some individuals were diagnosed with more than one NHL subtype, but this circumstance occurred most frequently with respect to other or unknown NHLs. We used the earliest diagnosis to determine NHL subtype when more than one subtype was indicated.

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

Because a few HBsAg-positive participants would not have had chronic infection (eg, because of 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 (ie, 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). SAS (version 9.1) was used for all analyses.

Role of the funding source

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

Results

603 585 eligible participants were tested for HBsAg at baseline health screening. 53 045 (9%) people were HBsAg positive. Table 1 shows baseline characteristics. HBsAg-positive individuals were more likely to be men and were younger than HBsAg-negative participants. Most participants were tested for HBsAg in 1992 or 1994—years when screening included mostly insured individuals rather than dependants. Alcohol use did not differ substantially with HBsAg status. Hepatitis was more frequent in HBsAg-positive than in HBsAg-negative participants, as manifested by abnormally raised ALT and AST concentration. Participants were followed up for a total of 8·0 million person-years (maximum 14 years).

Table 2 shows risks of various haematological malignancies in HBsAg-positive and HBsAg-negative participants. Among 1038 participants who developed NHL, 133 (13%) were HBsAg positive at baseline, and HBsAg positivity was associated with a significantly

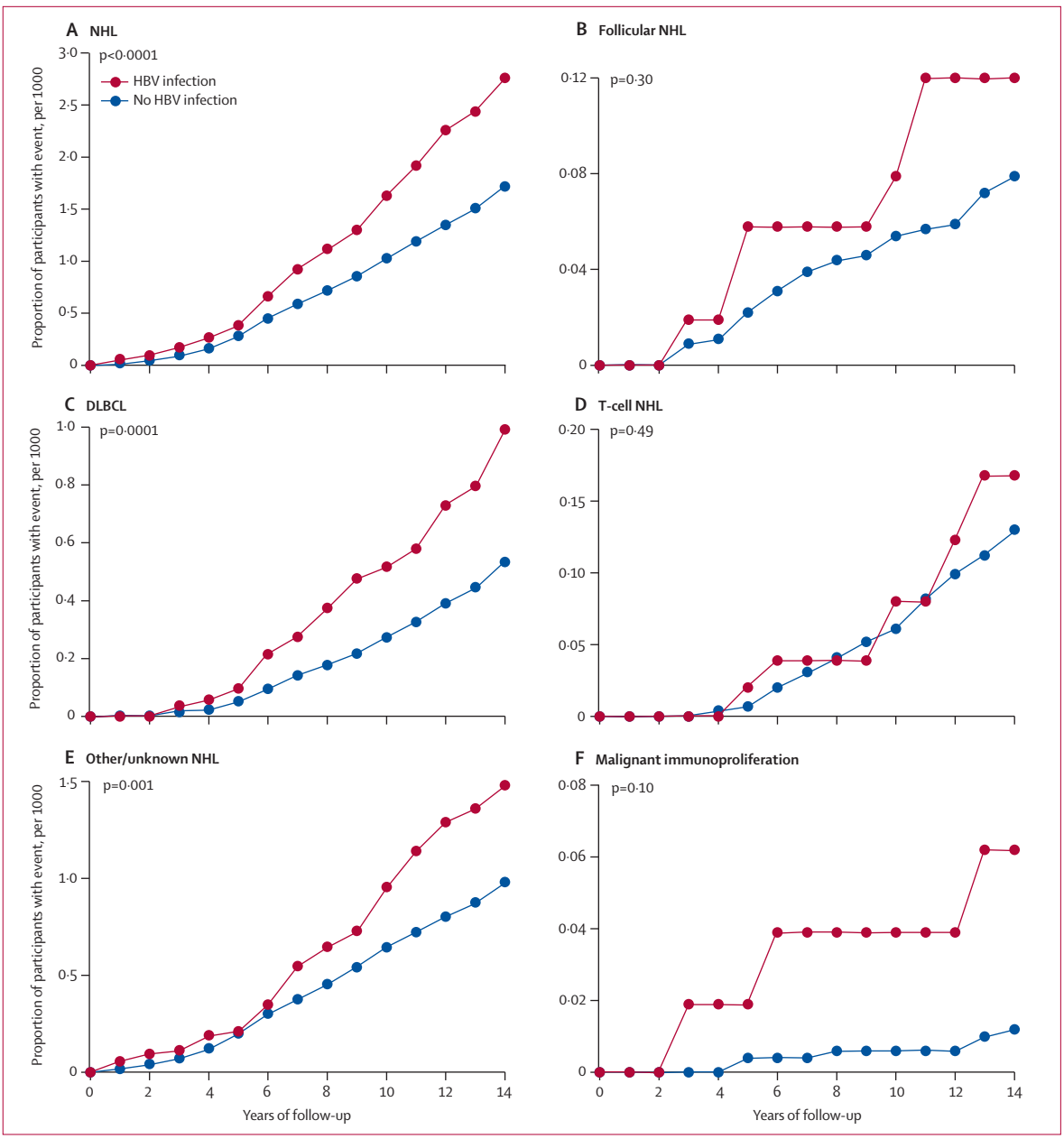

Figure: **Cumulative incidence of haematological malignancies in people with and without HBV infection in South Korea**
Results are shown for non-Hodgkin lymphoma (NHL) overall, four subtypes of NHL, and malignant immunoproliferation. Estimates were derived with lifetable methods. Red circles show data for people infected with hepatitis B virus (HBV), and blue circles show data for uninfected people. The vertical scale varies across the panels. p values are from the unadjusted Cox models presented in table 2.

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increased risk of NHL overall. An increased risk was significant only for the two most common NHL subtypes, DLBCL and other or unknown NHL. In the unadjusted model, HBsAg positivity was not significantly associated with increased risk of malignant immunoproliferation, Hodgkin's lymphoma, multiple myeloma, or various leukaemias (table 2). Notably, strength of associations with HBsAg increased after adjustment for sex, age, and calendar year of testing, and in the adjusted model, the association with malignant immunoproliferation was also significant. The association between HBsAg positivity and NHL was also seen in a sensitivity analysis in which we considered only outcomes recorded in inpatient records (table 2).

Risk of selected haematological malignancies is presented graphically in the figure. Risks of NHL (overall, DLBCL, and other or unknown NHL) and malignant immunoproliferation were higher in HBsAg-positive participants than in HBsAg-negative individuals throughout 14 years of follow-up. Specifically, a small difference in the proportion of participants with each outcome was apparent in the first few years after HBsAg testing, and this difference increased steadily with time. Likewise, the proportional hazards assumption was met for each outcome in table 2, showing that the effect of HBsAg positivity on risk of haematological 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 shows associations between abnormal test results for liver function and risk of various haematological malignancies. Participants with a raised AST concentration had an increased risk of NHL overall. Increased risks of multiple myeloma, lymphoid leukaemia, and myeloid or monocytic leukaemia were also recorded in association with AST elevation in the unadjusted model. However, these associations were attenuated when we adjusted for HBsAg status and demographic characteristics (table 3). Furthermore, the associations with multiple myeloma and leukaemias were weaker for ALT than for AST concentration (table 3). In the multivariate models that included liver function test results and HBsAg status, HBsAg positivity remained a significant predictor of increased NHL risk, whereas the associations with ALT

	Univariate model		Multivariate model*			
	Abnormal LFT		Abnormal LFT		HBsAg+	
	HR (95% CI)	p value	HR (95% CI)	p value	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's 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 leukaemia	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 leukaemia	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 leukaemia	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's 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 leukaemia	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 leukaemia	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 leukaemia	1·30 (0·82–2·05)	0·27	1·14 (0·72–1·82)	0·57	1·22 (0·77–1·94)	0·40

LFT=liver function test. HBsAg=hepatitis B surface antigen. +=positive. HR=hazard ratio. ALT=alanine aminotransferase. NHL=non-Hodgkin lymphoma. DLBCL=diffuse large B cell lymphoma. AST=aspartate aminotransferase. *The multivariate model includes the specified liver function test abnormality, HBsAg positivity, and adjustment for sex, age at baseline, and calendar year at baseline.

Table 3: **Associations of abnormal liver function test results and hepatitis B infection with risk of haematological malignancies**

and AST concentrations became attenuated (table 3). Finally, in a separate analysis restricted to HBsAg-positive individuals, NHL risk did not differ between those with increased liver function test results and those with normal liver function test results (data not shown).

Among 46 015 people who were HBsAg positive in 1992, 41 311 had another test in 1994, of whom 36 502 (88%) were HBsAg positive again (ie, had confirmed chronic infection) and the remainder were HBsAg negative. By comparison, of the 446 841 people who were HBsAg negative in 1992, 446 701 were either not retested in 1994 (439 643 participants) or were HBsAg negative again (7058 participants). In a sensitivity analysis in which we compared these two groups (ie, confirmed chronic infection *vs* no evidence of infection at either time), associations with haematological outcomes were similar to or slightly stronger than in the primary analyses. In particular, people with confirmed chronic HBV infection had an increased risk of 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 haematological 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 in people infected with HBV. A strength of our study was that HBV infection was documented prospectively, and we showed that the increased risk of NHL persisted during 14 years' follow-up. Furthermore, NHL risk remained raised after we adjusted for potential confounding factors including demographic characteristics, alcohol use, and abnormal liver function test results. We did not identify associations between HBsAg status and risk of Hodgkin's lymphoma, multiple myeloma, or leukaemia, suggesting that HBV does not contribute to development of these haematological malignancies, lending specificity to the association with NHL.

Previous studies of the association between HBV and NHL risk have been done in both HBV endemic countries (eg, South Korea, China) and non-endemic countries (eg, USA, Australia).[3–11] As discussed by Nath and colleagues,[22] results of 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 (200–600 cases) and have used unrepresentative convenience samples of controls (eg, patients admitted to hospital with cancer, blood donors). By comparison, large registry-based studies have provided mixed results. Results of a population-based case-control study of elderly adults in the USA (33 940 NHL cases) did not show associations between HBV infection and various specified NHL subtypes,[10] but HBV prevalence was very low (0·2%) and might have been under-ascertained. Two previous cohort studies of patients with HBV infection, similar in design to our study, but smaller, have also been reported. Ulcickas Yood and colleagues[11] noted an increased risk of NHL in a cohort of 3888 patients with HBV infection in a US health maintenance organisation (HR 2·30, 95% CI 1·01–5·24, based on eight NHL cases). By contrast, Amin and co-workers[23] reported no increase in NHL risk among 39 109 Australians reported to an HBV-infection registry.

The evidence from these studies, along with data from our study showing the presence of HBV infection more than a decade before NHL diagnosis, suggest that HBV might have a causal role in the development of NHL. If HBV infection causes NHL, the mechanism is unknown. One plausible mechanism could be chronic activation of B cells in HBV-related hepatitis, predisposing to DNA damage and transformation into lymphoma. Similar pathways have been proposed for HCV-mediated lymphomagenesis.[12,13,16] HBV DNA has been detected within peripheral blood B cells,[24] but whether HBV could directly transform lymphocytes is uncertain, because some results suggest that HBV is not present in NHL tumour cells.[4,5] In our study, NHL risk was increased in patients with raised ALT or AST concentrations, but the associations with HBsAg were not accounted for by these increases, since we noted an independent effect of HBsAg positivity in multivariate models. Furthermore, we did not record an additive risk of NHL in HBsAg-positive people with abnormal liver function test results. Likewise, Wang and colleagues[6] did not record an increased prevalence of serum HBeAg (a marker of high-level HBV replication and liver damage) in patients with NHL.

Because various NHL subtypes probably have differing causes,[25] a strength of our study was the availability of subtype data for a large fraction of NHL cases. We noted that HBsAg-positive individuals had an increased risk of DLBCL, the most common NHL subtype, which mirrors an association shown for HCV.[10,14,15] In our results, associations with follicular and T-cell NHLs were not significant. Associations with specific NHL subtypes should be interpreted with caution, because more than half of NHLs were coded as other or unknown subtype, and some people had more than one subtype (although in most instances, this situation occurred when there was both a specified subtype and an other or unknown subtype). We showed that HBsAg positivity was associated with significantly increased risk of other or unknown NHLs, and this association could probably be attributable to the presence of a large fraction of undiagnosed DLBCLs in this group. The group of other or unknown NHLs could also include cases of marginal zone and lymphoplasmacytic NHLs, which are low-grade NHL subtypes that have been associated with HCV.[10,14,15,26] Of interest, Fujimoto and colleagues[27] described an HBV-infected patient with splenic marginal zone NHL who developed a complete haematological remission after a flare of her infection, suggesting that the tumour was linked immunologically with the infection.

We noted an increased risk of malignant immunoproliferation in association with HBsAg positivity in

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analyses adjusted for sex, age, and enrolment year, although this finding is based on a small number of events. This finding is notable because this poorly specified category of neoplasms includes Waldenström macroglobulinaemia, which is essentially synonymous with lymphoplasmacytic lymphoma. Waldenström macroglobulinaemia and lymphoplasmacytic lymphoma have also been linked with HCV infection.[26] We are not aware of previous reports describing an increased risk of immunoproliferative disorders in patients infected with HBV, although the virus is associated with the occurrence of other immune-related disorders including polyarteritis nodosa, glomerulonephritis, and possibly essential mixed cryoglobulinaemia.[28]

Strengths and limitations of our study should be considered. Strengths include the large size of the KCPS cohort, which was representative of a large segment of the South Korean population, and the prospective documentation of HBsAg results. Although HBsAg was measured only once for most participants, South Korea has an endemic pattern of HBV infection, and most HBsAg-positive individuals probably had chronic infection that had been present since childhood and that persisted throughout follow-up.[17,21] Indeed, for a sizeable subset of participants, we were able to confirm that HBsAg positivity was chronic, and we showed that this group had similarly increased risk (or perhaps even higher risk) for NHL and malignant immunoproliferation compared with the main cohort. Unfortunately, we could not include additional serum markers (eg, HBeAg, HBV DNA) that would show severity of HBV infection. Our results are unlikely to be affected by confounding by infection with HCV or HIV, because these infections are rare in South Korea,[29,30] and we excluded people with evidence of these infections from our study sample. We used several systems of records to ascertain the occurrence of haematological malignancy, and we had sufficient data for 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, many cancer patients are at risk of developing severe HBV-related liver disease with initiation of chemotherapy, and this risk might be reduced with use of appropriate chemoprophylaxis with lamivudine.[31] In addition to the 13% of patients with NHL who we found to be HBsAg positive, many patients with NHL would be expected to have serological evidence of resolved HBV infection (ie, absence of HBsAg with antibody to HBV core antigen), although we did not have data for this group. Recent evidence points to a high risk of HBV reactivation in such patients in association with use of rituximab-containing chemotherapy regimens.[32,33] Lastly, even though we did not note an increased prevalence of HBsAg in association with other haematological malignancies, HBsAg prevalence was nonetheless as high among such individuals as in the Korean general population (roughly 9%). HBsAg-positive patients with these other malignancies would also be at high risk of HBV-related liver disease induced by cytotoxic chemotherapy. These considerations support systematic screening for HBV infection in patients with haematological malignancies who live in endemic regions or who have emigrated from these regions, and appropriate monitoring and prophylaxis of HBV-infected patients to mitigate HBV-induced liver disease arising during chemotherapy.[34]

Additional research is needed to clarify whether the association between HBV infection and NHL is causal. Even if the association proves causal, in view of the small magnitude of the association between HBsAg positivity and NHL risk, HBV infection would account for only a few NHL cases in endemic regions (eg, population attributable risk was 6% in our Korean cohort).[35] Thus, although universal HBV vaccination effectively prevents infection and greatly reduces the occurrence of liver cancer in endemic regions,[36] vaccination programmes would be expected to have a restricted effect on NHL incidence. Nonetheless, in people infected with HBV who develop NHL, HBV could account for a sizeable fraction of cases (eg, attributable risk was 43% in our cohort).[35] For HCV-infected patients with low-grade NHL (especially marginal zone lymphomas), HCV treatment seems effective for haematological remission.[37] Thus, we speculate that treatment directed at HBV in similar low-grade NHLs might lead to a clinical response and remove the need for chemotherapy. Further investigation in appropriate clinical series will be important.

Contributors

EAE was responsible for the study idea, undertook statistical analyses, and wrote the report. ERC was responsible for data management and did statistical analyses. SHJ was responsible for the study idea, did statistical analyses, and edited the report.

Conflicts of interest

The authors declared no conflicts of interest.

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