

Hepatitis B infection increases the risk of non-Hodgkin lymphoma: A meta-analysis of observational studies



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ARTICLE INFO

Article history:

Received 7 March 2013

Received in revised form 24 May 2013

Accepted 5 June 2013

Available online 26 June 2013

Keywords:

NHL

Hepatitis B

Diffuse large B-cell lymphoma

Non-Hodgkin lymphoma

Follicular lymphoma

T-cell lymphoma

ABSTRACT

Hepatitis B virus (HBV) infection is a major public health problem and the association between HBV infection and non-Hodgkin lymphoma (NHL) is unclear. The primary aim of our study was to evaluate the association between HBV infection assessed by a positive hepatitis B surface antigen (HBsAg) and the incidence of NHL and subtypes using a meta-analysis of epidemiological studies. The random effects model was used to calculate the outcome. Our search yielded 17 case-control and 5 cohort studies, including over 40,000 NHL cases. HBV infected individuals had an OR of 2.24 (95% CI 1.80–2.78; $p \leq 0.001$) of developing NHL. In high HBV prevalent countries, there were increased odds of diffuse large B-cell lymphoma and a trend toward increased odds of developing follicular and T-cell lymphoma. Future research is needed to better understand the biological mechanisms responsible for lymphomagenesis in patients with HBV infection.

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1. Introduction

Non-Hodgkin lymphoma (NHL) is the seventh most common cancer in the United States. Between 1975 and 2008 the average incidence of NHL rose by 2.4 percent per year and, in the last 5 years, has leveled off. In 2012, it was estimated that 70,130 people living in the United States would be diagnosed with NHL [1]. Both infectious and environmental etiologies have been implicated in the increased incidence of NHL, although over the last few decades there has been a decline in human immunodeficiency virus (HIV) related NHL [2]. Epstein-Barr virus, human herpes virus 8, human T-lymphotrophic virus type 1, *Helicobacter pylori* have all shown to be potential etiologies for NHL [3]. Two recent meta-analyses showed that patients with hepatitis C virus (HCV) had an increased risk of developing NHL raising the possibility of hepatitis B virus (HBV) as a potential risk factor for NHL [4,5].

Hepatitis B virus (HBV) is one of the leading causes of acute and chronic hepatitis worldwide. It is a small DNA virus that is a member of the *Hepadnaviridae* family. HBV is highly endemic in Asia, Africa, the Middle East, parts of Eastern Europe, and parts of South

America [6]. Recently, the World Health Organization has estimated that over two billion individuals are currently infected with HBV worldwide with around 350 million individuals with chronic HBV infection [7]. A mathematical model has estimated that there are 600,000 yearly deaths from HBV-related liver disease worldwide [8]. A recent meta-analysis of case control studies suggested an increased prevalence of HBV infection in patients with NHL but was unable to evaluate a relationship between HBV and NHL subtypes [9].

Given its chronic nature and increased prevalence, we hypothesized that HBV infection could be associated with an increased risk of developing NHL. The main aim of this study is to evaluate the association of HBV infection and NHL and its subtypes through a meta-analysis of epidemiological studies.

2. Materials and methods

2.1. Literature search

Two authors independently performed a computer-based literature search using PubMed/Medline and Google Scholar. The initial PubMed search with the combined term: (Hepatitis B or hepatitis) AND (lymphoma or risk of lymphoma or hematologic malignancies or lymphoproliferative disorders or non-Hodgkin lymphoma) resulted in 3040 returns through December 31, 2012. Titles and abstracts were then reviewed to determine if an article was relevant to our study. Full text articles of all selected studies were retrieved and if a paper was selected for inclusion, the bibliographic references were scrutinized to look for additional studies. A similar strategy was used to search Google Scholar, which revealed one additional return.

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2.2. Inclusion and exclusion criteria

An article was deemed relevant to our study if the article reported original data in English with human subjects and originated from epidemiologic observational studies. These studies could be case–control or cohort studies and needed to report an association between HBV infection and NHL. A definition of NHL was based on the World Health Organization classification system ($N=15$) or working formulation ($N=4$) in the majority of studies. All studies evaluating only Hodgkin lymphoma, multiple myeloma, or acute leukemia were excluded because of a different pathophysiology. Studies that were case series, case reports, review articles, and prior meta-analyses were excluded. Any discrepancies between the 2 reviewers on inclusion or exclusion of a study were resolved through consensus in all cases. If the same study population had multiple publications, only the most recent was selected. Older publications were used to clarify methodology or main characteristics of studied population, if necessary.

2.3. Data extraction

Two authors independently performed data extraction, which included author, title, year of publication, country of origin, sample size, inclusion and exclusion criteria, method for determining HBV status and method for diagnosis of NHL. For case–control studies, we extracted years of inclusion, the source and definition of cases and controls, the outcome measured with 95% confidence intervals (CIs), and the variables used for matching. For cohort studies, we extracted the source of the cohort, years of follow up, the outcome measured with 95% CIs, and the variables for adjustment. Any discrepancies between reviewers were addressed by a joint reevaluation of the original article. The characteristics and quality of the studies included in this meta-analysis, as well as their outcomes, will be presented in accordance to the checklist proposed by the Meta-analysis of Observational studies group [10].

2.4. Quality assessment

The quality of each study was assessed independently by two reviewers using the Newcastle–Ottawa Scale (NOS) [11]. The NOS uses 2 different tools for case–control and cohort studies and consists of 3 parameters of quality (selection, comparability, and exposure/outcome assessment). The NOS assigns a maximum of 4 points for selection, a maximum of 2 points for comparability, and a maximum of 3 points for exposure/outcome. Nine points is the highest score, reflecting the highest quality. We have considered a score above 6 as high quality.

2.5. Data analysis

Since the overall risk of NHL is low, the relative risk in prospective cohort studies mathematically approximates the odds ratio (OR), permitting the combination of case–control and cohort studies [12]. The primary outcome in this meta-analysis is reported as OR with 95% CIs of developing NHL in patients with HBV infection. The outcome was measured for the maximally adjusted association between HBV infection and NHL. We measured the outcome using the random effect model which accounts for heterogeneity between studies, which is expected in a study of this nature. Subset analyses were performed based on study type, specific type of NHL and by country according to their level of HBV prevalence. Countries were classified as low, intermediate, and high HBV prevalent based on a report on HBV prevalence from the Center for Disease Control and Prevention [13]. The two large European multi-country studies were placed in the low prevalent region based on the fact that the majority of the countries included were low prevalent areas. For analysis of specific type of NHL by HBV prevalence intermediate and low prevalence regions were combined because only one study reported specific types of NHL in the intermediate group [14]. Two studies reported a separate odds ratio for B-cell NHL and T-cell NHL and were used in the outcomes analysis as two distinct populations [14,15]. One study had two control groups and each was used as a distinct population during the outcomes analysis [16].

Heterogeneity between studies was assessed using the I^2 statistic [17]. Values of 25%, 50%, and 75% present mild, moderate, and severe heterogeneity, respectively. Since positive studies are more likely to be published than negative studies, the trim-and-fill method was used to address publication bias. The trim-and-fill method assumes that the effect sizes of all the studies distribute normally around the center of a funnel plot, and if asymmetry is found, it adjust for the potential effect that non-published (imputed) studies might have had on the measured outcome [18]. All calculations and graphs were obtained by using Comprehensive Meta-Analysis (CMA) version 2.2.050 (Biostat, Englewood, NJ).

3. Results

3.1. Search results

A total of 22 articles were selected for our meta-analysis. There were 5 prospective cohort studies [19–23] and 17 case–control

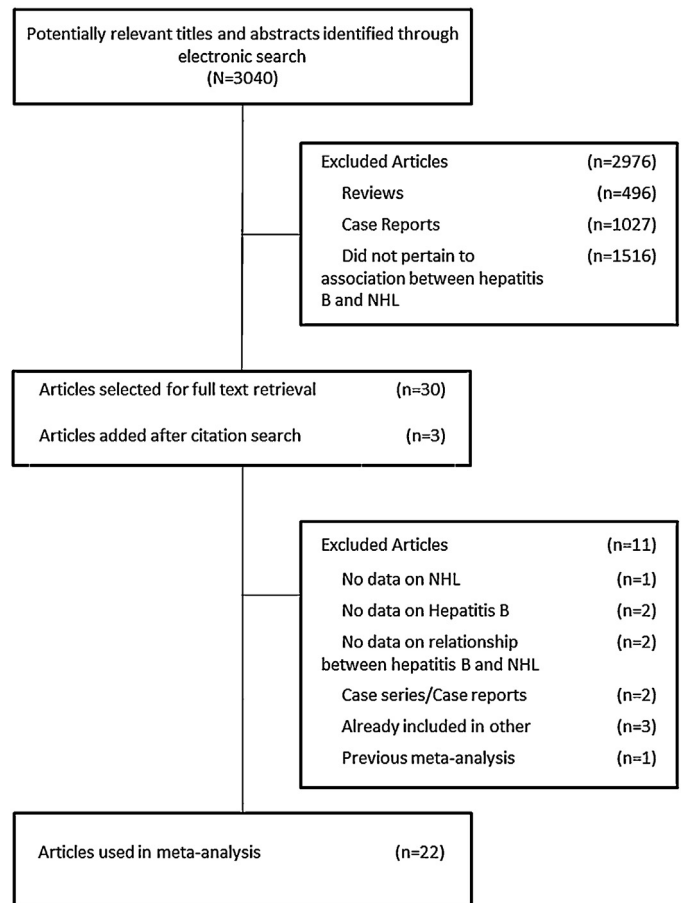


Fig. 1. Search results.

studies identified [6,14–16,24–36]. Our search flow is shown in Fig. 1.

3.2. Characteristics of the cohort studies

The main characteristics of the cohort studies are listed in Table 1. Studies were published between 2006 and 2012. Two studies originated from Asia [21,22], one from Australia [19], one from Europe [20], and one from the United States [23]. A total of 1377 cases of NHL in a cohort of 2,634,651 individuals, accounting for approximately 11 million person-years, were included in this meta-analysis.

3.3. Characteristics of the case–control studies

The main characteristics of the case control studies are listed in Table 2. A total of 42, 220 cases of NHL and 1,660,412 controls were included in the meta-analysis. Studies were published between 1999 and 2012. One study originated from the United States [24], four from Europe [26,28,31,36], two from Africa [27,32], and ten from Asia [6,14–16,25,29,30,33–35].

3.4. Quality assessment results

Fifteen case–control studies (88%) were of high quality (NOS > 6). Two studies (12%) had a score of 6 [27,34]. Seven case–control studies (41%) did not report how cases and controls were matched at trial design or if confounders were adjusted for during analysis [6,25–27,30,32,34]. The most common exposure bias was no designation of non-response rates in 8 studies (47%). In the cohort

Table 1
Main characteristics of cohort studies evaluating the association between hepatitis B virus infection and non-Hodgkin lymphoma.

Study	Year	Country (hep B prevalence)	Source of cohort	NHL assessment	Hep B assessment by seropositivity (Yes/No)	Median follow-up (years)	Follow Up period	Total cohort	Total person years	No. of patients with NHL	Adjustments
Amin et al. [19]	2006	Australia (Low)	NSW Health Department Notifiable Diseases Database	NSW Central Cancer registry	Yes	–	1990–2002	39,109	191,496	27	Age, sex, calendar year
Engels et al. [22]	2010	South Korea (High)	Korean Cancer Prevention Study cohort	National inpatient and outpatient databases	Yes	–	1992–2006	603,585	8,000,000	1038	Age, sex, calendar year
Fwu et al. [21]	2011	Taiwan (High)	Taiwan National Hepatitis B Vaccination Registry	National Cancer Registry	Yes	6.91	1983–2001	1,782,401	2,105,434	192	Age
Proby et al. [20]	2012	France (Low)	Viral Hepatitis Registry Côte d'Or	Hematological registry of Côte d'Or	Yes	6.15	1994–2005	465	2784	1	None
Yood et al. [23]	2007	USA (Low)	Henry Ford Health System and Kaiser Permanente Database	Henry Ford and Kaiser Permanente Tumor Registry	Yes	3+	1995–2001	209,091	802,510	119	Site, Age, sex, race, median follow up time, comorbidity index, income, hepatitis C infection

Abbreviations: NHL, non-Hodgkin lymphoma; Hep B, hepatitis B virus; HBsAg, hepatitis B surface antigen; NSW, New South Wales.

studies, all had NOS scores greater than 6. The most commonly found bias in four cohort studies (80%) was no statement stating the adequacy of follow up of the cohorts [19,21–23].

3.5. HBV assessment

All 5 cohort studies and 16 case control studies (95%) determined HBV status by seropositivity of at least the HBsAg. One case–control study (5%) determined HBV status by from Medicare diagnosis and/or billing records [24].

3.6. Outcomes results

The maximum adjusted association analysis showed an increased OR of developing NHL in patients with HBV infection (OR, 2.24; 95% CI 1.80–2.78; $P \leq 0.001$). The heterogeneity was high (85%). The trim-and-fill analysis identified four imputed studies, which would have not altered our results. When analyzing only cohort studies, an increased OR of developing NHL in patients with HBV was still seen (OR, 2.06; 95% CI 1.44–2.95, $P \leq 0.001$). Heterogeneity was moderate (67%) and the trim-and-fill analysis identified one imputed study, which would have not altered our results. In case control studies, there was an increased OR of developing NHL in patients with HBV (OR, 2.27; CI 1.74–2.94; $P \leq 0.001$). Heterogeneity was high (87%) and the trim-and-fill analysis identified two imputed studies, which would not have altered our results. Forest plots are shown in Fig. 2.

3.7. Subset analyses

Because of the difference in HBV rates in HBV high, intermediate, and low prevalence countries, subset analyses were done in high, intermediate, and low HBV prevalence populations. Subset analyses were also done between the major types of NHL, when reported, to see if associations were similar across diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and T-cell lymphomas (TCL).

3.7.1. NHL by region

Studies done in high HBV infection prevalent populations had an adjusted OR of NHL in patients with HBV of 2.51 (95% CI 2.01–3.13, $P \leq 0.001$) [6,15,16,21,22,25,32,33,35]. There was high heterogeneity (84%) but no publication bias was identified. In studies in intermediate HBV infection prevalent populations the adjusted OR of NHL in patients with HBV was 2.39 (95% CI 1.23–4.65, $P = 0.01$) [14,26,27,29,30,34]. Heterogeneity was high (75%) and no publication bias was identified. In studies in low HBV infection prevalent populations the adjusted OR of NHL in patients with HBV was 1.64 (95% CI 1.09–2.45, $P = 0.02$) [19,20,23,24,28,31,36]. Heterogeneity was high (72%) and trim-and-fill analysis identified three imputed study which made the results insignificant.

3.7.2. Diffuse large B-cell lymphoma

Eight studies [14,15,19,21,22,24,25,36] had information to evaluate DLBCL in patients with HBV with four studies [15,21,22,25] taking place in high HBV prevalent countries. The OR of DLBCL in patients with HBV was 1.84 (95% CI 1.13–3.01, $P = 0.01$). Heterogeneity was high (92%) and there was no publication bias identified. In the four studies done in high HBV prevalent countries, the OR of DLBCL in patients with HBV was 2.73 (95% CI 1.62–4.59, $P \leq 0.001$). Heterogeneity was high (92%) and there was no publication bias. In the four studies done in low/intermediate HBV prevalent countries, the OR of DLBCL in patients with HBV was 1.11 (95% CI 0.73–1.62,

Table 2

Main characteristics of case–control studies evaluating the association between hepatitis B virus infection and non-Hodgkin lymphoma.

Study	Year	Country (hep B prevalence)	Ascertainment period	Source of cases	No. of cases NHL	Source of controls	No. controls	Hep B assessment by seropositivity (Yes/No)	NHL assessment	Matching and adjustments
Anderson et al. [24]	2008	USA (Low)	1993–2002	SEER-Medicare Dataset	33,940	5% Random Sample from Medicare Beneficiary Database	122,531	No (Single Medicare Claim for Hep B)	ICD-O3 coding	Age, Gender, Selection Year
Becker et al. [36]	2009	Europe (Low)	1998–2004	Hospital or clinic based patients in Czech Republic, France, Germany, Ireland, Italy, and Spain	1209	Population registers in Germany and Italy. Hospital patients with diseases other than lymphoma in Czech Republic, Ireland, Italy, and Spain	34	Yes	Pathology confirmation all cases	Age, Gender, Country, Educational level
Chen et al. [25]	2008	Taiwan (High)	2000–2007	Taipei Veterans General Hospital newly diagnosed cases NHL	471	Non-lymphoma cancer patients, HBaAg (-) healthy volunteers	1013	Yes	Pathology confirmation all cases	Not reported
Cucuianu et al. [26]	1999	Romania (Intermediate)	1997–1999	Cancer Institute Cluj newly diagnosed B-cell NHL patients	68	Historical non hospitalized controls	943	Yes	Pathology confirmation all cases	Not reported
El-Sayed et al. [27]	2006	Egypt (Intermediate)	2002	Surgical pathology blocks from Natioal Cancer Institute, Cairo University	29	Healthy non hospitalized volunteers	36	Yes	Pathology confirmation all cases	Not reported
Franceschi et al. [28]	2011	Europe (Low)	1993–1998	Regional cancer registry, health insurances records, pathology registries	739	Cohort participants who were cancer-free, alive, and had blood samples available	1468	Yes	Pathology confirmation all cases	Center, age, sex, date within 3 months, time of day blood collected, fasting status
Iwata et al. [29]	2004	Japan (Intermediate)	1995–2001	Newly diagnosed cases of lymphoma at Toranomon Hospital	138	Patients at Toranomon Hospital admitted to orthopedics, ear, nose and throat departments	574	Yes	Pathology confirmation all cases	Age, sex, year of visit,
Kang et al. [15]	2011	South Korea (High)	1997–2008	Asan Medical Center pathology records	2442	Patients receiving general medical exams at Asan Medical center	15,562	Yes	Pathology confirmation all cases	Age, sex, year of serum collection
Kim et al. [16]–Control group 1	2002	South Korea (High)	1997–1998	Newly diagnosed NHL at Seoul National University Hospital	222	Non-hematologic malignancy diagnosed at Seoul National University Hospital	439	Yes	Pathology confirmation all cases	Age, sex, smoking, alcohol drinking, transfusion history, and anti-HCV antibody
Kim et al. [16] - Control Group 2	2002	South Korea (High)	1997–1998	Newly diagnosed NHL at Seoul National University Hospital	222	Non-Malignant admissions at Seoul National University Hospital	444	Yes	Pathology confirmation all cases	Age, sex, smoking, alcohol drinking, transfusion history, and anti-HCV antibody
Kuniyoshi et al. [30]	2001	Japan (Intermediate)	1990–1998	Newly diagnosed NHL at 3 hospital in Japan	348	Historical Blood donor data from Fukuoka Red Cross Center	1,513,358	Yes	Pathology confirmation all cases	Not reported
Lim et al. [6]	2007	Singapore (High)	2001–2005	Newly diagnosed NHL at the National Center of Singapore or department of hematology at Singapore General Hospital	498	Historical data from the Singapore National Health Survey	4698	Yes	Pathology confirmation all cases	Not reported

Marcucci et al. [31]	2006	Italy (Low)	1998–2001	Newly diagnosed NHL at 10 hospitals in Italy	399	Newly diagnosed other disease at the same 10 hospital in Italy	392	Yes	Pathology confirmed all cases	Age, Sex, level of education, place of birth
Mehdi et al. [32]	2006	Saudi Arabia (High)	1996–2004	Males with newly diagnosed NHL at two hospitals in central Saudi Arabia	565	Historical data on male blood donors	11,118	Yes	Pathology confirmed all cases	Not reported
Okan et al. [14]	2008	Turkey (Intermediate)	2003–2007	Hematology clinic at Gaziantep University newly diagnosed lymphoproliferative disorder	274	Patients recruited using records from university blood center	802	Yes	Pathology confirmed all cases	Age, sex
Park et al. [33]	2008	South Korea (High)	1998–2001	Newly diagnosed NHL at Korea Cancer Center Hospital	235	Newly diagnosed advance gastric cancer at Korea Cancer Center Hospital	235	Yes	Pathology confirmed all cases	Age, sex
Sonmez et al. [34]	2007	Turkey (Intermediate)	2002–2005	Newly diagnosed NHL at Black Sea Technical University Hospital	109	Patients from orthopedics, general surgery, urology, otorhinolaryngology clinics at same hospital	551	Yes	Pathology confirmed all cases	Not reported
Wang et al. [35]	2007	China (High)	2001–2006	Newly diagnosed NHL at Sun Ya-Sen University Cancer Center	586	Randomly chosen other individuals who were diagnosed with other cancers (except primary liver) at same hospital	1237	Yes	Pathology confirmed all cases	Age, sex

Abbreviations: NHL, non-Hodgkin lymphoma; Hep B, hepatitis B virus; ICD-O3, International Classification of Diseases for Oncology 3rd edition, SEER – Surveillance, Epidemiology, and End Results.

$P=0.62$). Heterogeneity was moderate (51%) and trim-and-fill analysis identified one imputed study which did not alter the results.

3.7.3. Follicular lymphoma

Eight studies [14,15,19,21,22,24,25,36] had information to evaluate FL in patients with HBV with four of these [15,21,22,25] in high HBV infection prevalent countries and zero in intermediate HBV infection prevalent countries. The OR of FL in patients with HBV was 1.66 (95% CI 1.02–2.70, $P=0.04$). Heterogeneity was moderate (66%) and trim-and-fill analysis identified one imputed study that did not change our results. In the four studies from high HBV prevalent countries, the OR of FL in patients with HBV was 1.99 (95% CI 0.91–4.38, $P=0.09$). Heterogeneity was moderate (71%) and trim-and-fill analysis identified one imputed study that would make our results significant (OR 2.35, 95% CI 1.15–4.81). In the four studies from low/intermediate HBV infection prevalent countries, the OR of FL in patients with HBV was 1.32 (95% CI 0.76–2.27, $P=0.32$). There was moderate (50%) heterogeneity and trim-and-fill analysis revealed one imputed study which would not have changed our results.

3.7.4. Chronic lymphocytic leukemia/Small cell lymphoma

Seven studies [14,15,20,21,24,25,36] had information to evaluate CLL/SLL in patients with HBV with three of these [15,21,25] being in high HBV infection prevalent countries. The OR of CLL/SLL in patients with HBV was 1.32 (95% CI 0.76–2.30, $P=0.33$). There was moderate heterogeneity (48%) and there was no publication bias. In the three studies from high HBV infection prevalent countries, the OR of CLL/SLL in patients with HBV was 1.78 (95% CI 0.72–4.43, $P=0.21$). There was no heterogeneity and no publication bias. In the four studies from low/intermediate HBV infection prevalent countries, there was moderate heterogeneity (681%) with an OR of CLL/SLL in patients with HBV of 1.24 (95% CI 0.58–2.65, $P=0.57$). There was no publication bias reported.

3.7.5. T-cell lymphoma

Ten studies [14–16,19,22,24,25,33,35,36] had information to evaluate TCL in patients with HBV, with six [15,16,22,25,33,35] conducted in high HBV prevalent countries. The OR of TCL in patients with HBV was 1.44 (95% CI 1.08–1.91, $P=0.01$). Heterogeneity was low (27%) and trim-and-fill analysis revealed two imputed studies which would have not changed our results. In the six studies from high HBV prevalent countries, the OR of TCL in patients with HBV was 1.39 (95% CI 0.95–2.03, $P=0.10$). Heterogeneity was moderate (50%) and trim-and-fill analysis revealed three imputed studies which would have made our results significant (OR 1.60, 95% CI 1.13–2.27). In the four studies from low/intermediate HBV prevalent countries, the OR of TCL in patients with HBV was 1.41 (95% CI 0.80–2.48, $p=0.23$). There was no heterogeneity and trim-and-fill analysis revealed two imputed studies which would not have changed our results. Table 3 shows complete results of OR for NHL and subtypes in patients with HBV infections.

3.8. Sensitivity analysis

When excluding the one study that did not test HBV status with seropositivity [24], the overall results were similar. The OR of NHL in patients with HBV was 2.34 (95% CI 1.90–2.89, $P\leq 0.01$), heterogeneity was high (82%) and trim-and-fill analysis revealed three imputed studies which would have not changed our results. When excluding the three studies [25,27,34] with NOS scores less than seven, the overall results were similar. The OR of NHL in patients with HBV was 2.35 (95% CI 1.87–2.96, $P\leq 0.01$), heterogeneity was high (93%) and trim-and-fill analysis revealed four imputed studies

Table 3

Meta-analysis evaluating the adjusted association between HBV infection and NHL subtypes and by region.

Type	Overall odds ratio	High prevalence countries odds ratio	Intermediate prevalence countries odds ratio	Low prevalence countries odds ratio
NHL	2.24 (95% CI 1.80–2.78) ($P \leq 0.001$) $n = 22$	2.51 (95% CI 2.01–3.13) ($P \leq 0.001$) $n = 9$	2.39 (95% CI 1.23–4.65) ($P = 0.01$) $n = 6$	1.64 (95% CI 1.09–2.45) ($P = 0.02$) $n = 7$
DLBCL	1.84 (95% CI 1.13–3.01) ($P = 0.01$) $n = 8$	2.73 (95% CI 1.62–4.59) ($P \leq 0.001$) $n = 4$	^a	1.11 (95% CI 0.73–1.69) ($P = 0.62$) $n = 4$
FL	1.66 (95% CI 1.02–2.70) ($P = 0.04$) $n = 8$	1.99 (95% CI 0.91–4.38) ($P = 0.09$) $n = 4$	^a	1.32 (95% CI 0.76–2.27) ($P = 0.32$) $n = 4$
CLL	1.32 (95% CI 0.76–2.30) ($P = 0.33$) $n = 7$	1.78 (95% CI 0.72–4.43) ($P = 0.21$) $n = 3$	^a	1.24 (95% CI 0.58–2.65) ($P = 0.57$) $n = 4$
T-cell	1.44 (95% CI 1.08–1.91) ($P = 0.01$) $n = 10$	1.39 (95% CI 0.95–2.03) ($P = 0.10$) $n = 6$	^a	1.41 (95% CI 0.80–2.48) ($P = 0.23$) $n = 4$

NHL, non-Hodgkin lymphoma; DLBCL, diffuse large b-cell lymphoma; FL, follicular lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic leukemia; CI, confidence interval.

^a Included in low prevalence group for subset analysis.

which would have not changed our results. Sensitivity Analysis of NHL subtypes is reported in Table 4.

4. Discussion

Several environmental and pathologic etiologies have been shown to be potential risk factors for developing NHL including blood transfusions, diabetes, and multiple viral illnesses [3,37–39]. HIV, Epstein-Barr virus, HTLV-I, HHV-8 and *Helicobacter pylori* are all established risk factors for developing NHL [40]. Hepatitis viruses including HBV and HCV have both been shown to be increased in patients with NHL with a suspected causal relationship. Our study showed that there was a 2.24 times increase in the odds of developing NHL in patients with HBV infection when combining both case-control and cohort studies suggesting that HBV infection may be a risk factor for developing NHL.

In subtype analysis, there was a statistical risk of developing DLBCL, FL, and TCL in patients with HBV infection while there was no statistical risk of developing CLL/SLL. When looking at studies done in high, intermediate or low HBV prevalent countries, there was a similar statistically significant risk of developing NHL. In DLBCL there was a statistical risk in high HBV infection prevalent populations with no statistical risk seen in low HBV infection prevalent populations. In FL and TCL there was a trend toward risk in high HBV infection prevalent populations with no statistical risk seen in low HBV infection prevalent populations. The odds of CLL/SLL were not increased in either high or low HBV infection prevalent populations. The increased risk of DLBCL in patients with HBV virus infection could be driven by the increased number of chronic HBV infections in highly prevalent countries. This

population is potential for further research to show a biological relationship between HBV and DLBCL, FL, or TCL.

There has been little research done into mechanisms by which HBV may cause lymphomagenesis. Many hypotheses exist and it is likely that both viral and host factors are likely factors for HBV leading to NHL. First, chronic HBV may 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 [16,41–43]. This may result in chronic stimulation of B-cells which may predispose to DNA damage and transformation into B-cell NHL. Other investigators have also speculated that an immunologic response to chronic local antigenic stimulation caused by HBV infection may be associated with development of lymphoma [44]. Similar pathways have been proposed for HCV-mediated lymphomagenesis [45,46]. HBV-encoded X protein (HBx) has been shown in liver cells to inhibit p53 and lead to abnormal liver cell division leading to hepatocellular carcinoma [35,47–50]. A similar mechanism of inhibition of p53 in B-cells by HBV-encoded proteins like HBx, may contribute to malignant transformation and to the development of B-cell NHL [35,41,43,49]. Similarly, it has been suggested that HBV infection of endothelial cells might serve as a trigger for expression, production, or release of hematopoietic tumor growth factors which stimulate cell proliferation [31]. An indirect role may be through HBV-specific immune-mediated cell injury which has been shown in the process of HBV-induced hepatocellular carcinoma [42]. Another theory is that an unknown virus with a mode of transmission similar to HBV might be transmitted with HBV and be responsible for lymphomagenesis, though no virus has been found to date [16,40,43]. Finally, the immunodeficiency predisposing patients with HBV may play a role in lymphomagenesis though no link has been proven [29].

Our study has several strengths. First, it is the largest study to date that evaluates the association between HBV infection and NHL. Our study included both case control and cohort studies while a prior meta-analysis only looked at case control studies [9]. Second, the majority of our studies were of high quality based on the NOS and after a sensitivity analysis was done excluding studies with NOS < 7 the main association between HBV infection and NHL remained unchanged. Third, our study was the first to indicate that association of HBV infection and NHL subtypes might vary in high and low HBV prevalent countries. Finally, study level data allowed for meaningful analysis in NHL subtypes and by HBV high, intermediate, and low prevalent regions.

However, our study has limitations that are based on the quality of the published studies. First, although the majority of studies used seropositivity to diagnose HBV infection one study used database records to ascertain HBV status. After conducting a sensitivity analysis excluding this one study, there remained a statistically

Table 4

Sensitivity analysis of meta-analysis evaluating the adjusted association between HBV infection and NHL subtypes by type of sensitivity analysis.

Type	OR for studies assessing HBV status with seropositivity	OR for studies with NOS > 7
NHL	2.34 (95% CI 1.90–2.89) ($P \leq 0.001$)	2.35 (95% CI 1.87–2.96) ($P \leq 0.001$)
DLBCL	2.05 (95% CI 1.25–3.35) ($P \leq 0.001$)	1.84 (95% CI 1.04–3.26) ($P = 0.04$)
FL	1.71 (95% CI 0.95–3.09) ($P = 0.07$)	1.73 (95% CI 0.98–3.05) ($P = 0.06$)
CLL	1.61 (95% CI 0.93–2.81) ($P = 0.09$)	1.40 (95% CI 0.77–2.56) ($P = 0.27$)
T-cell	1.49 (95% CI 1.10–2.00) ($P = 0.01$)	1.43 (95% CI 1.03–2.00) ($P = 0.03$)
Excluded Study	[24]	[25,27,34]

NHL, non-Hodgkin lymphoma; DLBCL, diffuse large b-cell lymphoma; FL, follicular lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic leukemia; CI, confidence interval.

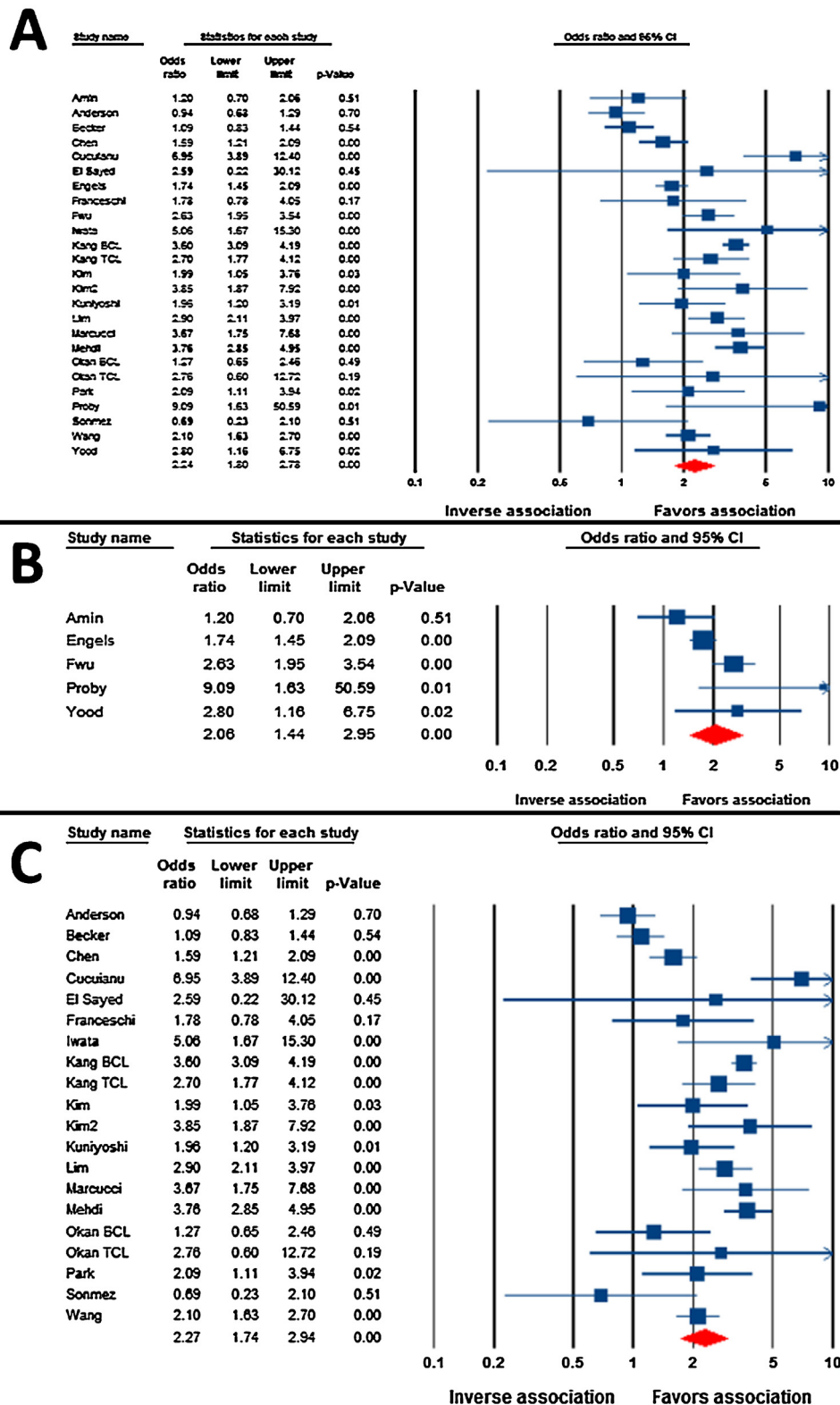


Fig. 2. Estimates of the odds ratio of developing non-Hodgkin's lymphoma in patients with Hepatitis B virus by (A) all studies, (B) cohort, (C) case-control studies.

significant risk of developing NHL and DLBCL and a trend toward significance in FL and TCL in patients with HBV infections. Further, from the manuscripts included in this study we were unable to determine if HBsAg seropositivity indicated acute or chronic HBV infections and HBsAg seropositivity may underestimate the real association between HBV and NHL, if occult hepatitis infection is

considered. Occult HBV infections have been defined for patients that test negative for HBsAg but positive for HBV-DNA in serum or tissues or both [51]. Recent data shows that occult HBV infection may further add to the association of HBsAg-positive HBV and CLL/SLL [25,35]. It is also possible that persons could be positive for HBV-DNA in hepatocytes or lymphocytes but be negative in

the serum [43]. Further research is needed to determine the relationship between occult HBV infections and NHL. Third, not all the studies controlled for potential confounding variables such as autoimmune infections, HIV status, age, and socioeconomic status. Three cohort studies also did not specify the adequacy of follow up of the cohort patients, which could underestimate the true incidence of NHL or HBV infections in these patients. In case control studies, the lack of specification of adjustments or matching of cases and controls may have led to an overstatement of the risk of developing NHL in patients with HBV. Finally, many of the NHL subtypes analyses, although specified *a priori*, had small sample sizes and should be interpreted with caution.

In conclusion, our study suggests that HBV infection increases the risk of developing NHL, DLBCL, FL, and TCL while not increasing the risk of CLL/SLL. The increased risk of DLBCL in patients with HBV infection only seems to hold true in high HBV infection prevalent populations and further research is needed to determine if the increased risk is because of the larger number of HBV infections in these areas or because of a true causal relationship. Future research focusing on the lymphomagenesis is needed to establish a biological relationship between HBV infection and developing NHL. If a link is found, early vaccination programs of at risk populations may decrease the rates of NHL in patients with HBV infections, or treatment of latent HBV may help with containment of NHL especially in chronic forms of the disease such as FL or CLL/SLL.

Conflicts of interest statement

J.J.C has research grants from GlaxoSmithKline and Millennium Pharmaceuticals and all other authors have no conflict of interest to declare.

Acknowledgements

None. No funding to declare. *Contributions:* S.D. and L.S. designed the research. S.D. and J.C. collected data. J.J.C. performed statistical analysis and all authors interpreted data, wrote, reviewed, and approved the final manuscript submitted.

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