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Original Article

Association of risk of non-Hodgkin's lymphoma with hepatitis B virus infection: a meta-analysis

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Abstract: Objective: A meta-analysis was carried out to systematically evaluate the correlation between hepatitis B virus (hepatitis B virus, HBV) infection and risk of non-Hodgkin's lymphoma (non-Hodgkin lymphoma, NHL). Methods: We searched Medline, EMBASE, PubMed, Cochrane Library, Chinese Biomedical Literature Database, Chinese Journal Full-text Database, Chinese scientific journals full text databases and collected information about HBV infection and risk of NHL associated case-control studies. Two reviewers extracted useful information which were included in the study independently, and Revman 5.2 was used for meta-analysis. Results: A total of 24 studies were included in this research. Meta-analysis showed that among all of the included studies the heterogeneity were existed (I^2 = 76%, P<0.05). With random effects model the OR was 2.39 (95% CI, 1.93-3.96), indicating infection rate in NHL patients with HBV was higher than that in the control group. Subgroup analysis according to ethnicity suggested that HBV infection were associated with NHL risk both in Asian (OR = 2.46, 95% CI: 2.01, 3.00, P<0.001) and Caucasian (OR = 2.15, 95% CI: 1.37, 3.37, P<0.001) population. Conclusion: HBV infection may increase the risk of NHL, but it still need a large number of experiments and epidemiological studies to verify.

Keywords: Non-Hodgkin's lymphoma, Hepatitis B virus, risk, meta-analysis

Introduction

Hepatitis B virus (hepatitis B virus, HBV) infection has become a major public health problem in the world [1]. There were about $ 350 million chronically infected patients worldwide [2]. There were about 62 million people each year died of liver disease that associated with HBV infection [3]. The hepatitis B infection situation in China is more severe [4]. Lymphoma accounted for the eighth in our common malignancies, which accounted for the fifth most common malignancy in the United States [5]. In recent years, its incidence is rising. Lymphoma were divided into Hodgkin's lymphoma (Hodgkin lymphoma, HL) and non-Hodgkin's lymphoma (non-Hodgkin lymphoma, NHL) two kinds by World Health Organization. Genetic, environmental and infectious factors together caused lymphoma [6]. NHL etiology is not fully understood. We have come to realize that different subtypes of NHL prognosis were different, and the causes may be different. HBV infection caused only not damage the liver, but also caused systemic reactions. There was a higher HBV DNA detection rate in peripheral blood mononuclear cells. NHL patients receiving chemotherapy may cause latent infection of HBV reactivation, and it can even lead to acute liver failure in severe cases. In recent years, a large number of studies concentrated on the correlation between incidence of HBV infection and lymphoma. However, the result is often inconsistent. In this study, we carried out the relevant case-control meta-analysis in order to provide a basis for clinical diagnosis and treatment decisions.

Materials and methods

Literature searching and screening

"hepatitis B virus, hepatitis B, hepatitis B", and "lymphoma, lymphoma", were set as the key words and literatures were retrieved from Medline, EMBASE, PubMed, Cochrane Library databases, Chinese Biomedical Literature Database, Chinese Journal Full-text databases

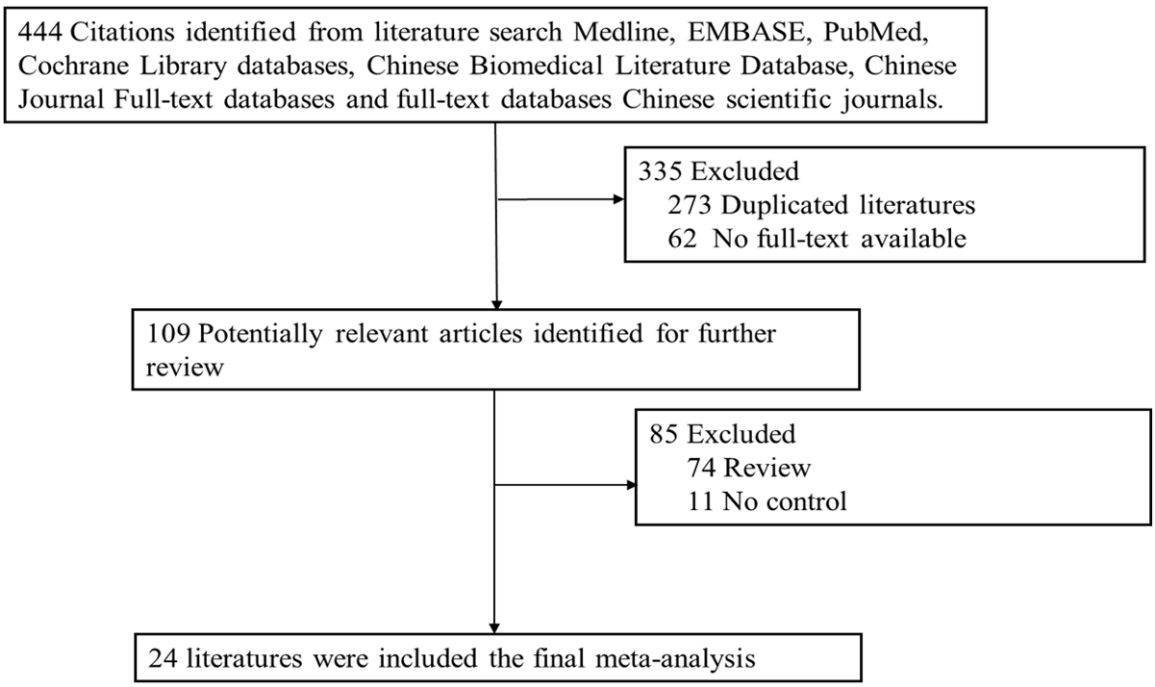

Figure 1. The flow chart of literature identified.

Table 1. Characteristics of the included studies

First author	Publication Year	Country	Ethnicity	Number of case	Number of control	OR	95% CI
Anderson et al.	2008	USA	Caucasion	33940	122531	0.92	0.70-1.22
Becker et al.	2012	Germany	Caucasion	1518	1496	1.59	0.65-3.90
Becker et al.	2009	European	Caucasion	2362	2465	1.8	1.17-2.76
Cocco et al.	2008	Italy	Caucasion	164	334	1.71	0.80-3.65
Cuculanu et al.	1999	Romania	Caucasion	68	943	6.96	3.89-12.40
El-Saued	2006	Egypt	Caucasion	29	36	2.59	0.22-30.12
Franceschi et al.	2011	European	Caucasion	739	2028	2.55	1.12-5.81
Kang et al.	2011	South Korea	Asian	2094	15562	4.3	1.59-14.52
Kim et al.	2002	Italy	Caucasion	222	883	2.26	1.39-3.67
Kim et al.	2011	South Korea	Asian	344	404	2.26	1.39-3.67
Kuniyoshi et al.	2001	South Korea	Asian	348	1513358	1.96	1.20-3.19
Lim	2007	Singapore	Asian	556	4698	2.68	1.97-3.65
Luo et al.	2011	China	Asian	316	316	2.71	1.72-4.27
Luol et al.	2010	China	Asian	1279	1340	1.5	1.21-1.87
Lwata et al.	2004	Japan	Asian	145	574	4.8	1.59-14.52
Ma et al.	2010	China	Asian	67	67	3.19	1.16-8.75
Marcucci et al.	2006	Italy	Caucasion	399	392	3.23	1.61-6.46
Mehdi	2006	Saudi Arabia	Caucasion	565	11118	3.76	2.85-4.95
Park et al.	2008	South Korea	Asian	235	235	1.86	1.02-3.37
Qin et al.	2007	China	Asian	109	128	4.14	2.21-7.75
Sonmez	2007	Turkey	Caucasion	109	551	0.69	0.24-1.99
Wang et al.	2007	China	Asian	586	1237	2.16	1.70-2.75
Yan et al.	2009	China	Asian	132	132	4.04	2.00-8.16
Zhang et al.	2010	China	Asian	129	129	2.83	1.37-5.83

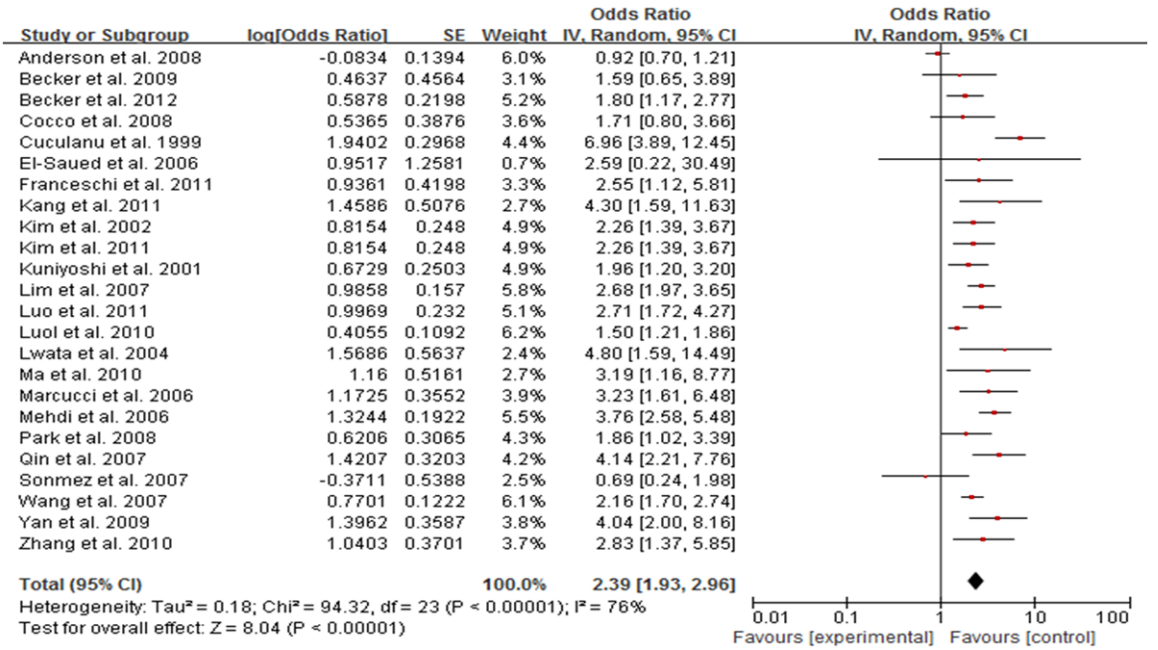

Figure 2. Forest plot of the relation between HBV infection and NHL risk in total population.

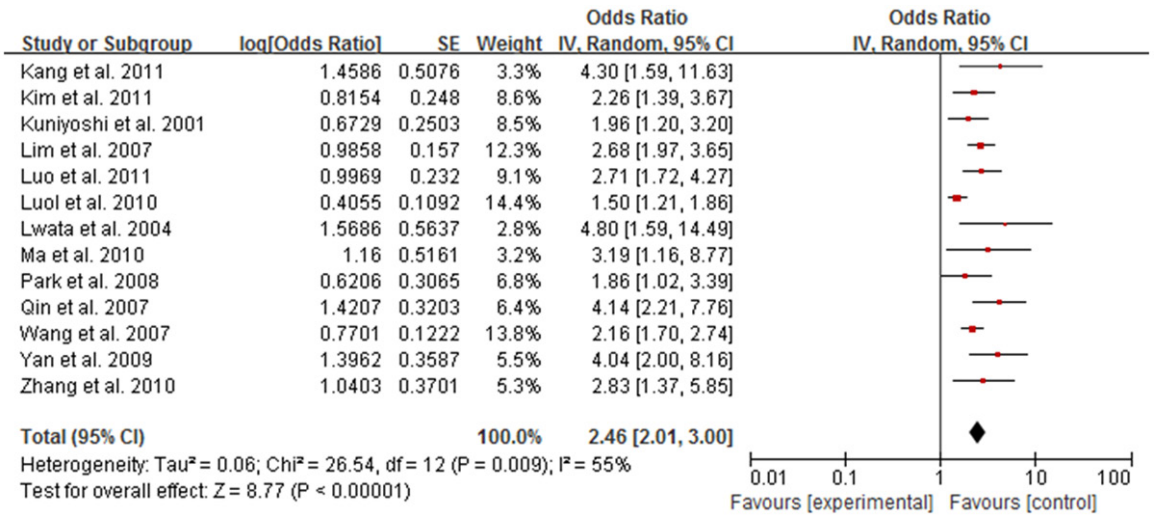

Figure 3. Forest plot of the relation between HBV infection and NHL risk in Asian population.

and full-text databases Chinese scientific journals. At the same time we retrieved literatures from the world's major academic institutions website ASCO, EMSO, NCCN, and Google, Medical Matrix and other searching engines were used to find the relevant literature on the Internet.

Literature inclusion and exclusion criteria

Inclusion criteria: literatures about the correlation between HBV infection and incidence of NHL case-control study and nested case-control study; NHL patients were confirmed by cytology or pathology; Hepatitis B virus infection was defined as a serum HBsAg positive; Languages were English and Chinese; Patient's race, nationality, age and geographical were not limited; In literatures there were sufficient data to calculate the odds ratio (odd radio, OR) and 95% confidence intervals (confidence intervals, C1) to assess the infection difference in NHL group compared with the HBV infection in the control group.

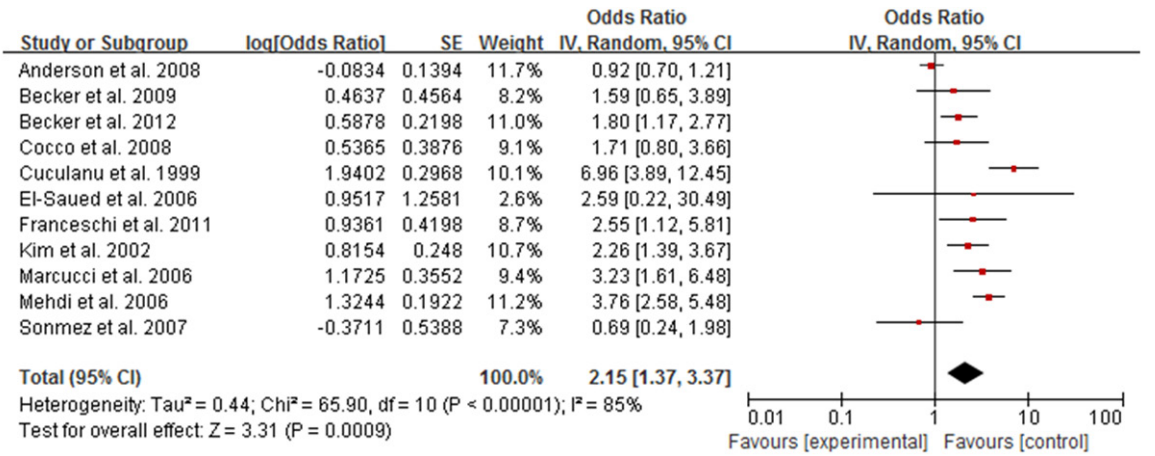

Figure 4. Forest plot of the relation between HBV infection and NHL risk in Caucasian population.

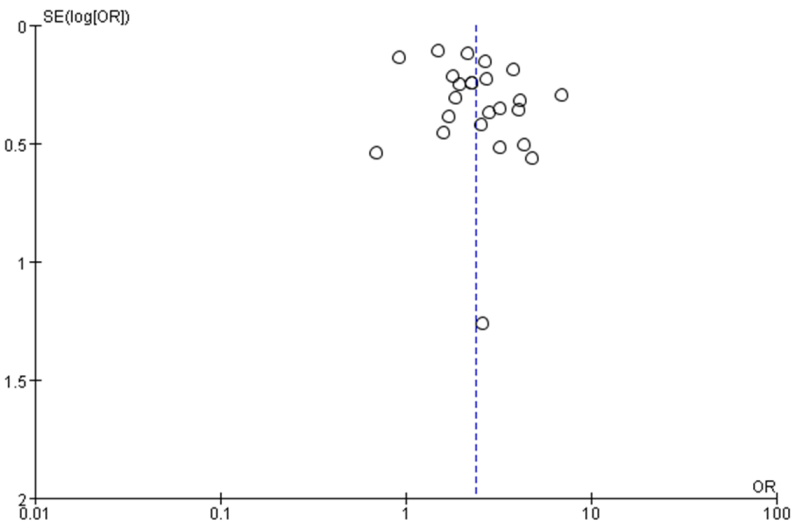

Figure 5. Funnel plot for publication bias tests.

Exclusion criteria: The descriptions only concentrated on infection rate of HBV in patients with NHL while there was no descriptive study in control group. The literatures only concentrated on HL patients or there was no distinguish between NHL and HL patients; there was no clear definition on HBV infection or the definition was any one of the five items in two pairs of semi-detection was positive in literatures.

Based on the above criteria, two investigators read literatures independently from title and abstract to full text and screened the literatures layer by layer. For example, they first read the title and summary of the obtained documents and excluded the literatures which obviously did not meet the inclusion criteria. Then they read the full text of the document which may meet the inclusion criteria to identify whether the literature truly meet the inclusion criteria. If there were controversies or differences in determining whether they meet the inclusion criteria, a third investigator was enrolled in to decide whether to include it. For repetitive published literatures, we selected the latest and most comprehensive reports.

Finally two researchers extracted information from the included literatures independently, including the first author's name, publication date, race, region, the source of patients in the control group, age, sex, the number of non-HBV-infectious and HBV infectious in the control and case group. They filled the form, extracted the table, and did cross-check, and then finally reached consensus.

Statistical analysis

Heterogeneity between the studies were assessed and calculated by Q test. Finally we calculated the combined value of OR and 95% CI in the studies to assess the correlation between risk of NHL and HBV. When P was less than 0.05 in z test, the combined OR values showed statistical significance. When there

was no heterogeneity between studies (P>0.1, I^2<50%), fixed effects model was used for meta-analysis in each study. If there is heterogeneity (P<0.1, I^2>50%), the random effects model was used, and subgroup analyzes were based on possible sources of heterogeneity. Funnel plot was used to assess publication bias. In Egger test when P<0.1, publication bias showed statistical significance. The two researchers input the data into Revman 5.2 and did meta-analysis independently and finally they achieved the consistent results.

Results

Literature search results and the feature of research

444 documents were obtained after initial screening; by reading titles, abstracts and full text, duplicate publication was excluded, and according to the inclusion criteria and exclusion criteria, through primary screening and secondary screening, ultimately 24 literatures [7-30] were included, the flow chart as shown in **Figure 1**. A total of 46, 455 NHL patients and 1, 680, 957 controls were included (**Table 1**).

Meta-analysis results

Meta-analysis showed that, HBV infection rate in NHL patients was higher than that in the control group, with statistical significance. Meta-analysis showed that among all of the included studies the heterogeneity were existed (I^2 = 76%, P<0.05). With random effects model the OR was 2.39 (95% CI, 1.93-3.96), indicating infection rate in NHL patients with HBV was higher than that in the control group (**Figure 2**). Subgroup analysis according to ethnicity suggested that HBV infection were associated with NHL risk both in Asian (OR = 2.46, 95% CI: 2.01, 3.00, P<0.001, **Figure 3**) and Caucasian (OR = 2.15, 95% CI: 1.37, 3.37, P<0.001, **Figure 4**) population.

Publication bias of the included literature

Funnel plot was used to test the publication bias of all included studies. Funnel plot shape of all included studies prompted no obvious asymmetry (**Figure 5**), suggesting no obvious publication bias.

Discussion

At present, there are a large number of reports on the correlation between pathogen infection and the incidence of lymphoma, such as Epstein-Barr virus and Hodgkin's lymphoma, Burkitt's lymphoma and primary central nervous system lymphoma, human T-cell leukemia virus type 1 (HTLV-1) and T lymphocytic leukemia, and Helicobacter pylori and gastric lymphoma [31-35]. HBV is a hepatotropic virus, and it also has a pro-lymphocyte characteristic. In the case of undetectable HBV antigen, expression of HBV DNA and HBV antigen is often detectable in peripheral mononuclear cells and lymphoid tissues. HBV infection can stimulate the expression, production and release of hematopoietic tumor growth factor; long-term chronic stimulation results in clonal expansion of lymphocytes. In addition, HBV DNA can also be integrated into the lymphocyte cell genome, thereby activating Bc1.2 oncogene or leading to its translocation.

The study screened and obtained the literature meeting the requirements of quality through comprehensive literature collection, and strict inclusion and exclusion criteria. Meta-analysis results suggest that, HBV infection rate in NHL patients was about 2.39 times of that in the control group. Because there is a higher prevalence of HBV infection in patients with NHL, the results of this study is important for clinical treatment. It has been reported that when NHL patients receiving immunosuppressive chemotherapy, there was a risk of HBV reactivation; the patient may appear asymptomatic elevated ALT, fatigue, nausea, vomiting, jaundice and other manifestations of viral hepatitis; severe cases may even appear peritoneal effusion, coagulation abnormalities, hepatic encephalopathy and other signs of liver failure. HBV reactivation leads to the interruption of antitumor therapy, seriously affecting its therapeutic effect and increasing mortality. Therefore, it needs careful measurement of HBV infection for NHL patients before chemotherapy; Lamivudine may play a preventive role when infected patients receiving chemotherapy.

This article included a larger number of patients and involved a wider scope, providing a strong support for the reliance of results. But there are

still some limitations. Firstly, the included studies had statistical heterogeneity; although there was no statistical heterogeneity among nested case-control studies after subgroup analysis, most of the literature did not match the age and gender, and liver diseases were not classified; NHL typing was also not performed, and the merger of HCV infection was not clear; at the same time, control populations included healthy populations and other cancer patient populations; these factors can affect the reliability of the results. Secondly, there is not enough data to assess the effect of environmental factors on the correlation between HBV and NHL risk. Finally, although no significant publication bias had been found by statistical test, the results of this paper were still possibly false positive because of some unpublished negative results. Given the limitations of literature included in this study may affect the authenticity of the conclusions of this study to a certain extent, we look forward to conducting a large sample study based on the case-control studies with more rigorous design and higher quality to further confirm the results.

The results of the study showed that there was a higher infection rate of HBV in patients with NHL; before chemotherapy, the use of lamivudine can prevent viral reactivation and liver failure in patients with HBV infection during chemotherapy; while whether HBV infection was one of the reasons for NHL incidence needs further research to confirm.

Disclosure of conflict of interest

None.

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