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Hepatitis C virus infection is a risk factor for non-Hodgkin lymphoma
A MOOSE-compliant meta-analysis

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Abstract

Previous studies have reached conflicting results regarding the possibility that hepatitis C virus (HCV) infection may increase the risk of non-Hodgkin lymphoma (NHL). We performed a meta-analysis to clarify the relationship between HCV infection and development of NHL. The PubMed, Web of Science, and Embase databases were searched for relevant studies estimating the association between HCV infection and NHL risk through October 31, 2017. Fixed effects or random effects models were used to calculate the pooled odds ratio (OR) and its 95% confidence interval (CI). A total of 18 studies met the inclusion criteria. We found a positive association between HCV infection and NHL (pooled OR 1.69, 95% CI 1.40–2.03, $P < .05$). In conclusion, our meta-analysis suggested that HCV infection was associated with increased risk of developing NHL.

Abbreviations: CI = confidence intervals, HCV = hepatitis C virus, OR = odds ratio, RR = relative risk.

Keywords: hepatitis C virus, meta-analysis, non-Hodgkin lymphoma, risk

1. Introduction

Non-Hodgkin lymphoma (NHL) is a malignant tumor of lymphoid tissue.[1] Several microbial infections (eg, hepatitis virus, human immunodeficiency virus, Epstein Barr virus, human T-cell leukemia virus, *Helicobacter pylori*), exposure to toxic pesticides, and lifestyle factors such as poor diet are closely related to the occurrence of NHL.[2,3] Hepatitis C virus (HCV) is an RNA virus of the family Flaviviridae,[4] and is involved in the development of primary mixed type cold globulin and lymphoid tissue hyperplasia, which can further evolve into lymphoma.[5] As far back as the early 1990s, studies identified that patients with NHL had a higher rate of HCV infection, suggesting that there was a close association between these 2 conditions, yet failed to clarify the causal relationship between them.[6] Subsequently, additional epidemiological studies were conducted to investigate the potential relationship between HCV infection and NHL, but yielded inconsistent results.[7–24] Some studies suggested that HCV infection is a risk factor for NHL[8,10,12,14–16,21,23,24] while others have reached the opposite conclusion.[7,9,11,13,17–20,22] Therefore, in order to clarify whether the HCV infection is a risk factor for NHL, it is first necessary to establish a theoretical basis for the causal relationship between these conditions. The purpose of this study was to systematically review the relationship between HCV infection and NHL, perform a meta-analysis, and reach more reliable conclusions regarding the potential association of these 2 conditions.

2. Materials and methods

2.1. Study selection

We searched the PubMed, Web of Science, and Embase databases to identify articles analyzing the association between HCV infection and NHL through October 31, 2017. Studies had to be indexed with a MeSH heading of "Lymphoma, non-Hodgkin" and "hepatitis C virus" in combination with any keywords. The references of all resulting studies were searched for other potentially relevant studies.

Because the data included in this study were retrieved from published literature, ethical approval was not required.

2.2. Study inclusion and exclusion criteria

Eligible studies included in this meta-analysis had to meet all of the following criteria:

(1) the study analyzed the association between HCV infection and development of NHL using a case–control or cohort study design;
(2) the study fully reported either relative risk (RR) or odds ratio (OR); and
(3) the study was published in Chinese or English full text.

Studies meeting any of the following criteria were excluded:

(1) the study design was a literature review, case report, basic animal experiment, conference paper, or letter;
(2) the study analyzed exposures that were not HCV infection or outcomes that were not NHL;
(3) the study reported RRs or ORs incompletely; or
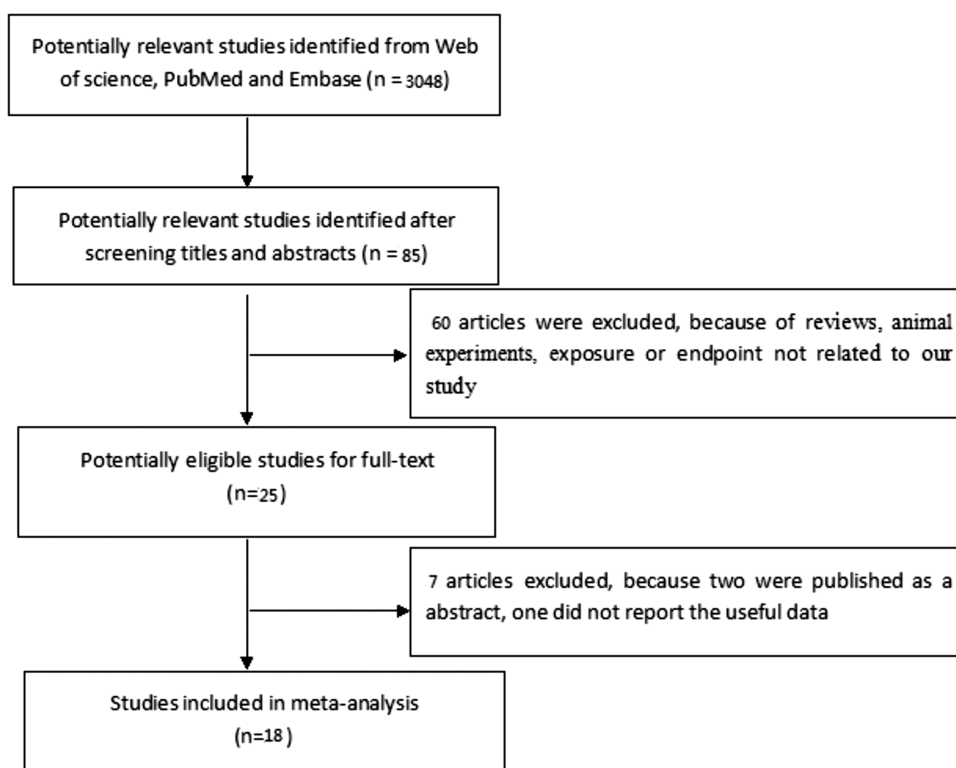(4) the study was not published in Chinese or English full text.

Figure 1. The flow chart of literature filtering.

2.3. Data abstraction

Three investigators abstracted the data independently using a standard information extraction form. Data abstracted from each study included: name of the first author, year of publication, study population, age distribution of the study population, the number of NHL cases, the total number of individuals studied, the OR or RR and their 95% confidence intervals (CIs), the date that participants entered the study, and the document quality score.

2.4. Statistical analysis

We evaluated the association between HCV infection and development of NHL using ORs and their 95% CIs. If no or minor heterogeneity was apparent ($P > .05$, $I^2 < 50\%$), a pooled OR was calculated using a fixed effects model. If significant heterogeneity was evident ($P < .05$, $I^2 > 50\%$), then the pooled OR was calculated using a random-effects model. Sensitivity analyses were conducted to explore the impact of each study on the pooled OR. Finally, to test for publication bias in the funnel plot, Begg and Egger tests were used. P values $< .05$ were considered statistically significant. All statistical analyses were conducted using STATA 12.0.

3. Results

3.1. Study retrieval

After searching and scanning 3048 study abstracts, we eliminated reviews, animal experiments, conference papers, letters or studies involving irrelevant exposures and outcomes. After reading the titles and abstracts, most of these were excluded, leaving 18 studies.[7–24] The study search process is shown in Figure 1.

3.2. Included studies

According to the inclusion and exclusion criteria, 18 studies were included in the meta-analysis, covering a time period from 1999 to 2017. Eight reports were of cohort studies[7–13,18] and the remaining 10 reports were of case–control studies.[14–17,19–24] The studies examined different populations in Western countries. All included studies had a high-quality score. The basic characteristics of the included studies are shown in Table 1.

3.3. Meta-analysis

We conducted a meta-analysis of the 18 included studies. We found that HCV infection was significantly associated with risk of NHL in 8 studies,[8,10,12,14–16,21,23,24] while the remaining 10 studies suggested HCV infection was either not associated with increased risk of NHL or was associated with a reduced risk.[7,9,11,13,17–20,22] Significant heterogeneity was observed among studies ($I^2 = 68.5\%$, $P < .05$), and thus a random effects model was used to calculate a pooled OR. We found that HCV infection was associated with increased risk of NHL (pooled OR = 1.69, 95% CI 1.40–2.03, $P < .05$). This result suggested that patients with HCV infection were more likely to develop NHL. The results of the meta-analysis are shown in Figure 2.

We also evaluated the association between HCV infection and risk of NHL using subgroup analyses. We found that HCV infection was associated with increased risk of NHL not only in cohort studies but also in case–control studies (OR = 1.26, 95%

Table 1

The characteristics of included studies.

Study, yr	Population	Study design	Sample size (n) case/control or total	Adjusted OR (95% CI)	Quality score
Ohsawa et al (1999)	Japanese	Cohort	4/2162	2.10 [0.57, 5.38]	8
Cowgill et al (2004)	Egyptian	Case–control	220/222	2.90 [1.90, 4.50]	6
Morton et al (2004)	American	Case–control	464/534	1.90 [0.50, 7.30]	6
Dubergl et al (2005)	Swedish	Cohort	20/27150	1.99 [1.21, 3.07]	7
Amin et al (2006)	Australian	Cohort	33/75834	0.90 [0.60, 1.20]	8
Sanjose et al (2008)	American, Australian, European	Case–control	4784/6269	1.78 [1.40, 2.25]	6
Sch€ollkopf et al (2008)	European	Case–control	2819/1856	2.20 [0.90, 5.30]	6
Spinelli et al (2008)	Canadian	Case–control	795/697	2.57 [0.89, 7.44]	6
Franceschi et al (2011)	European	Cohort	9/737	1.30 [0.55, 1.30]	7
Giordano et al (2010)	American	Cohort	319/146394	1.28 [1.12, 1.45]	7
Omland et al (2010)	Danish	Cohort	3/4204	1.89 [0.39, 5.52]	7
Richiardi et al (2010)	Italian	Case–control	91/182	1.30 [0.50, 3.20]	6
Proby et al (2012)	French	Cohort	6/1259	3.42 [1.25, 7.45]	7
Cerhan et al (2014)	American	Case–control	1591/6746	2.02 [1.47, 2.76]	6
Mbulaiteye et al (2016)	American	Case–control	295/21818	4.10 [1.10, 15.40]	6
Taborelli et al (2016)	Italian	Case–control	571/1004	2.39 [1.66, 3.43]	6
Mahale et al (2017)	American	Case–control	1623538/200000	1.57 [1.34, 1.84]	6
Wang et al (2017)	European	Cohort	310/52479	0.46 [0.40, 1.12]	8

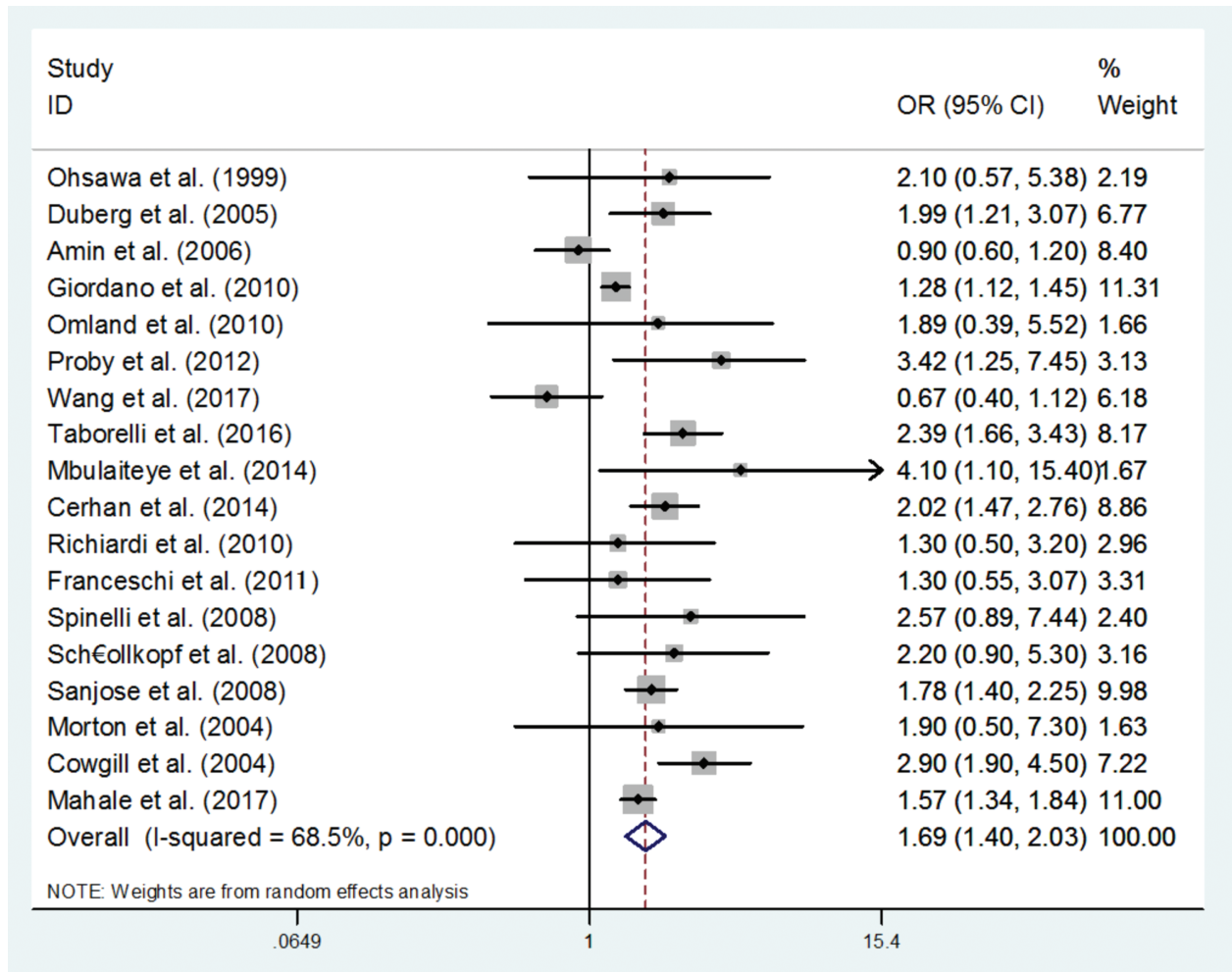CI = confidence interval, OR = odds ratio.

Figure 2. The effect of hepatitis C virus infection on the risk of non-Hodgkin lymphoma.
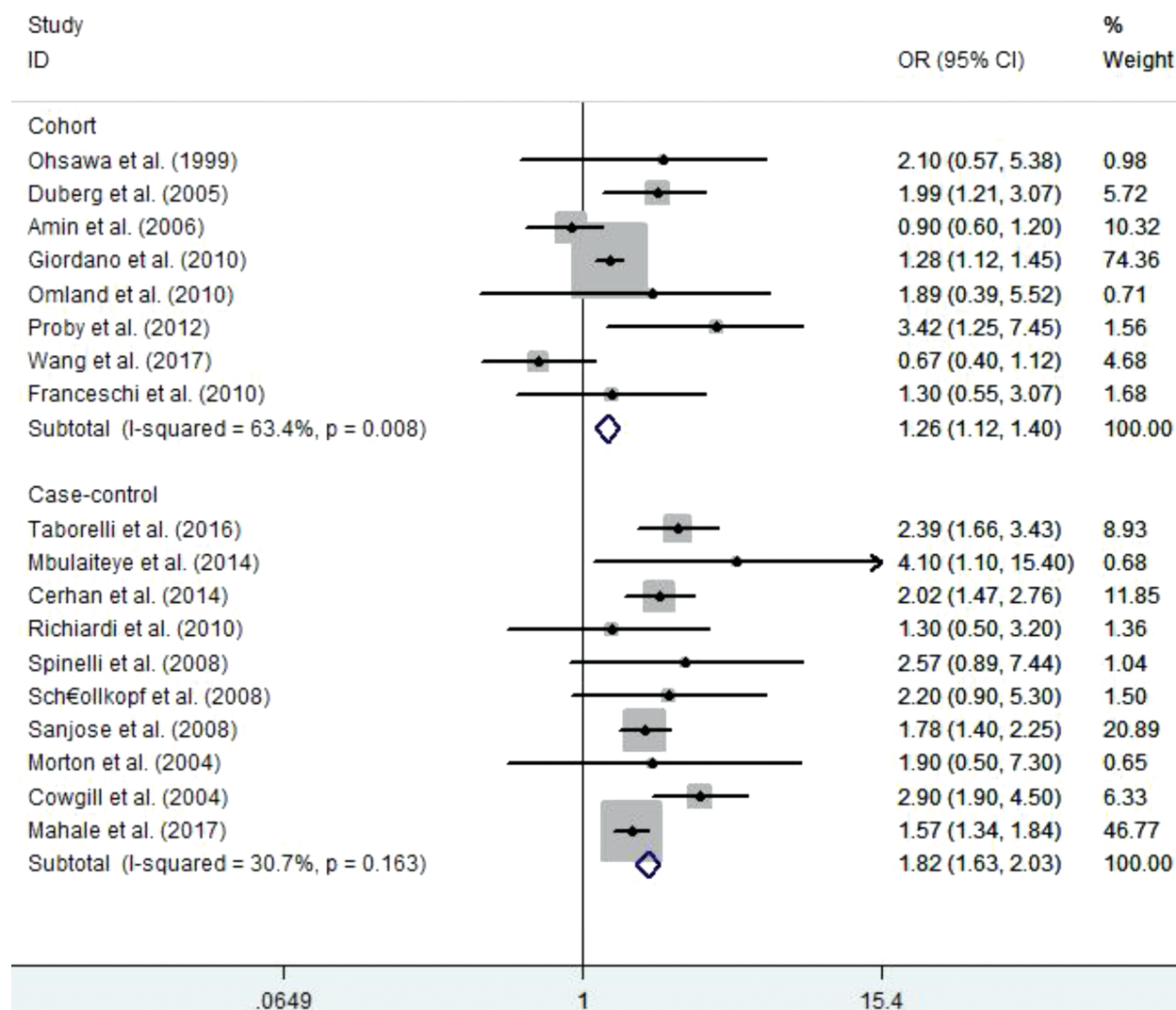
Figure 3. The subgroup analysis with the effect of hepatitis C virus infection on the risk of non-Hodgkin lymphoma according to study design.

CI 1.12–1.40 and OR = 1.82, 95% CI 1.63–2.03, respectively). The results of subgroup analyses are shown in Figure 3.

3.4. Sensitivity analysis

In order to investigate the effect of each of the included studies on the pooled OR, we excluded the case–control studies, which had little effect on the overall result. This finding suggested that the risk of developing NHL in individuals with HCV infection was significantly higher than in uninfected individuals. The results of sensitivity analyses are shown in Figure 4.

3.5. Assessment of publication bias

We used a funnel plot, Begg test and Egger test to assess the presence of publication bias. As shown in Figure 5, the included studies were broadly distributed across the funnel area. Moreover, Egger test showed no evidence of publication bias ($P = .16$). In summary, there was relatively low potential of publication bias among the included studies.

4. Discussion

In this systematic review meta-analysis, we found that HCV was significantly associated with risk of NHL. Compared with uninfected individuals, the risk of NHL was 69% higher among individuals with HCV infection.

The specific causal relationship between HCV infection and NHL remains unclear, but 2 possible biological mechanisms can be proposed. First, persistent HCV antigen stimulation during chronic infection may play an important role in the amplification of initial polyclonal B cells, which can lead to autonomous B-cell proliferation, immune dysfunction, and the eventual occurrence of B-cell malignancies.[25] Quinn et al found that the HCV E2 envelope glycoprotein was an important viral antigen that induced B cell proliferation.[26] In fact, the B-cell receptors (BCRs) of B-cells that cause HCV-associated lymphoma are often specific for the HCV E2 envelope glycoprotein. This result strongly supports the hypothesis that lymphocyte proliferation is involved in HCV-related NHL. B-cells respond to the E2 envelope glycoprotein of HCV through their specific BCRs, which can be activated by
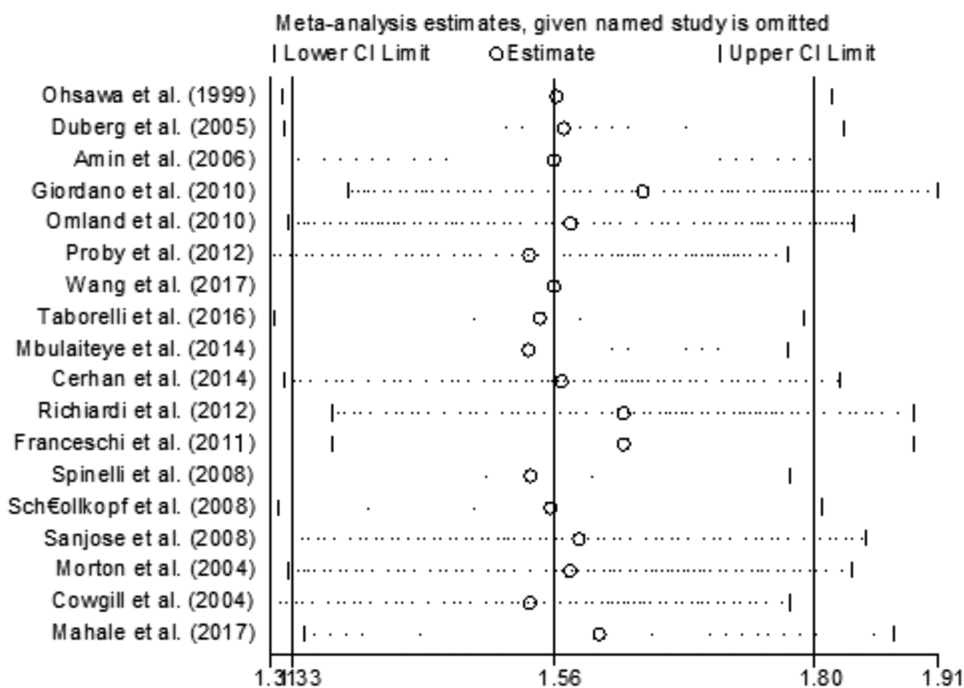
Figure 4. Sensitivity analysis forest plots.

2 signaling complexes (BCR and the CD19/CD21/CD81 complex), increasing the risk of B-cell malignancy. In addition to the dual stimulation hypothesis.[27] Levy et al also proposed the virus entry theory, in which B cells bind virions through these 2 receptors, effectively enabling viral internalization and leading to genomic instability, mutation of oncogenes, and development of malignant lesions. However, NHL patients with HCV infection receiving antiretroviral therapy still developed malignant tumor despite the reduction of virus load.

Second, cytokine imbalances may lead to some autoimmune and lymphoid tissue diseases. Cytokines may be the key factors in the pathogenesis of HCV-associated lymphoid tissue diseases. Mixed cryoglobulinemia is a predecessor of lymphoma, and this condition has been widely used for characterization of cytokine production in HCV-associated lymphoid tissue disease. CXCL13 is a positive regulator in patients with mixed

Figure 5. Forest plot for publication bias.

cryoglobulinemia while BCA-1 and BLC regulate B cell transport regulator.[28] Antollie et al found different cytokines and chemokines in the serum of patients with mixed cryoglobulinemia and proposed that CXCL-10 and CXCL-11 have a potential role in the pathogenesis of mixed cryoglobulinemia.[29–31]

Compared with previous observational studies, our study had some advantages. First, 18 studies were included, which greatly increased the sample size, and made the conclusion more reliable. Second, all included studies were of high methodological quality. Thus, this meta-analysis should provide reliable evidence to inform epidemiological studies of the relationship between HCV infection and NHL.

However, our study also had some limitations. First, most of the included studies were conducted in European and American populations. People in different areas, with different dietary and lifestyle habits (for example, a high-fat diet) might have different baseline risk of NHL.[30] Thus, it is difficult to know whether our results can be generalized other populations. Second, most of the included studies did not distinguish between gender, but hormone levels also affect risk of NHL.[31] Third, HCV infection might have different influences on the distinct pathological types of NHL. Among HCV-infected individuals, the risk for diffuse large B-cell lymphoma was 4 times higher than the risk for follicular lymphoma. Fourth, previous epidemiological studies showed a significant association between HCV infection and NHL risk in areas with high HCV incidence (such as Japan and Italy) but there was no clear correlation observed in regions with low endemicity.[32] Therefore, there might be strong regionality in the association between HCV infection and NHL.[6] However, most of the included studies were conducted in European countries and had obvious geographical distributions. Fifth, significant heterogeneity was observed in the meta-analysis, and we considered the following factors might be potential explanations:
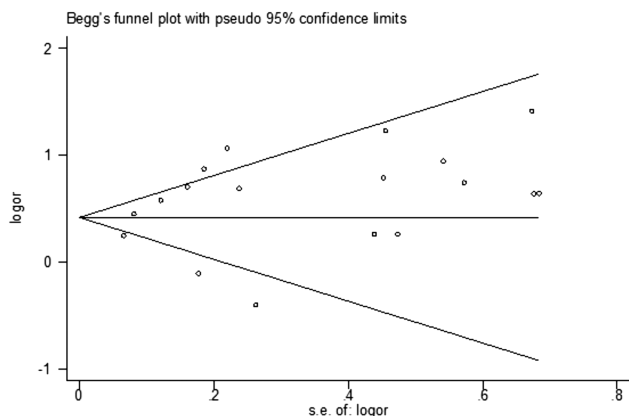
(1) the included studies were based on different populations with different gender compositions;
(2) the quality of the included studies differed; and
(3) the pathological types of NHL studied were different.

5. Conclusions

In summary, this systematic review and meta-analysis suggested that HCV infection significantly increased the risk of NHL. However, multicenter, larger studies in other populations are still needed.

Author contributions

Data curation: Xiaofeng Zhu, Li Jing.
Formal analysis: Xiaofeng Zhu, Li Jing.
Investigation: Xiaofeng Zhu.
Methodology: Xiaoming Li, Xiaofeng Zhu, Li Jing.
Project administration: Xiaofeng Zhu.
Writing – original draft: Xiaofeng Zhu.
Writing – review and editing: Xiaoming Li.

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