Effect of hepatitis C virus infection on the risk of non-Hodgkin's lymphoma: A meta-analysis of epidemiological studies

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Although a high prevalence of hepatitis C virus (HCV) infection among non-Hodgkin's lymphoma (NHL) patients had been reported, subsequent epidemiological studies conducted to examine a causal association between HCV and NHL have provided inconsistent results across studies. A strikingly positive association has been reported primarily from Italy and Japan, while no association was found in other regions of the world. To clarify the association between HCV and NHL, we conducted a systematic literature review. Eligible study designs were nested case-control studies, population-based case-control studies, and hospital-based case-control studies using non-cancer subjects as controls. The studies published through January 1991 to August 2003 were searched through Medline. Ultimately, 23 studies with 4049 NHL patients and 1,813,480 controls were identified. Summary statistics were crude odds ratios (ORs) comparing the anti-HCV seropositive and seronegative subjects. As we identified heterogeneity between studies, summary statistics were calculated based on a random-effect model. We did not find any evidence of publication bias. The major sources of variation were the use of blood donor controls and year of publication. The summary OR for NHL was 5.70 (95% confidence interval (CI), 4.09–7.96, *P*<0.001). The subgroup analysis by phenotype showed a similar trend for B-cell (5.04, 95% CI: 3.59–7.06) and T-NHL (2.51, 95% CI: 1.39–4.56). In conclusion, we found a strongly positive association between anti-HCV seropositive test subjects and risk of NHL. Further biological studies examining this association are warranted. (Cancer Sci 2004; 95: 745–752)

Non-Hodgkin's lymphoma (NHL) is a set of malignant diseases arising from lymphoid tissues. As it is heterogeneous in terms of classification and has relatively low incidence, epidemiological studies regarding causative factors for NHL have not been satisfactorily conducted compared with other malignant diseases. However, several possible causative factors have been identified, including pesticides, blood transfusion, immunodeficiency, radiation, smoking and several types of diet, as summarized elsewhere.[1)] Among them, infectious agents, such as *Helicobacter pylori*, human T-cell leukemia virus (HTLV-I), and human immunodeficiency virus (HIV), are promising factors from the viewpoint of prevention.

Hepatitis C virus (HCV) is a hepatotrophic virus contributing to the development of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Extrahepatic manifestations resulting from HCV, including lymphoproliferative syndromes such as type II mixed cryoglobulinemia (MC),[2)] have received increased attention. High prevalence of HCV infection among NHL patients was reported in the early 1990s,[3)] suggesting a causal association between HCV and NHL. Subsequent epidemiological studies examined this potential association, but yielded inconsistent results across studies. The studies reporting a significantly positive association are from HCV endemic areas such as Italy and Japan, while other studies reporting no association come from non-endemic countries.[4)]

The aim of this study is to clarify the association between HCV infection and risk of NHL by means of a systematic review of the literature.

Materials and Methods

Selection of studies. We used Medline to identify articles published between January 1990 and August 2003, indexed with a MeSH heading of 'Lymphoma, non-Hodgkin' and 'hepacivirus,' in combination with the keywords 'cohort studies' and 'case-control studies.' The inclusion criteria for our analysis were 1) studies reporting odds ratio (OR) or risk ratio (RR) calculated by comparing the HCV positive category to the negative category as a measure of association, 2) study designs: cohort study, nested case-control study, population-based case-control studies, hospital-based case-control study, 3) studies using non-cancer controls, and 4) studies using HCV antibody test. All potentially relevant articles were reviewed by two or three independent investigators (K.M., A.K., and A.S.) and disagreement was resolved by discussion between the investigators. The reference lists of the studies identified through the search process were also checked in order to thoroughly identify candidate studies. We identified 25 candidate papers[3, 5–28)] including an in-press report by one of us[27)] through the selection process. Two of them[3, 19)] were excluded from our analysis because those papers were presenting the same data by the same authors.[5, 20)] The studies included in our study are listed in Table 1.

Data abstraction. Three investigators (K.M, A.K., and A.S.) abstracted the data independently using a standard information extraction form. Characteristics abstracted from the articles included: the name of the first author, country of study, year of publication, study design, case definition, control definition, inclusion/exclusion criteria, methods of HCV measurements, matching factors, numbers of cases and controls, and HCV test results. The definition of HCV-positive in our study was a positive HCV antibody test in any type of antibody test, including second- and third-generation-enzyme-linked-immunosorbent assay (ELISA)/enzyme-immunoassay (EIA) and recombinant immunoblot assay (RIBA). We contacted the authors of studies containing relevant information who did not report their results in a way convenient for our analysis. Therefore, data used in our analysis do not necessarily match to those published in the original reports. Those who provided additional information on their work are acknowledged.

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Table 1. Summary of studies that have examined the association between HCV infection and non-Hodgkin's lymphoma

	Country	Cases (*n*)	HCV positive case (*n*)	Case description	B-NHL subgroup analysis	T-NHL subgroup analysis	Control (*n*)	HCV positive control (*n*)	Control descrption	Matching	HCV tests
Ferri *et al.* (1994)	Italy	50	15	B-cell NHL only	Yes	No	30	1	Hospital-based control	Age	2G ELISA and RIBA
Silvestri *et al.* (1996)	Italy	366	31	NHL	Yes	Yes	6917	199	Population-based control in a cohort	No	2G EIA and RIBA
Musto *et al.* (1996)	Italy	150	40	NHL	No	No	466	25	Hospital-based control	No	3G ELISA
Mazzaro *et al.* (1996)	Italy	199	57	NHL	No	No	6917	199	Population-based control in a cohort	No	2G EIA and RIBA
De Rosa *et al.* (1997)	Italy	100	21	NHL	Yes	Yes	1568	30	Blood donor control	No	3G ELISA and RIBA
Zuckerman *et al.* (1997)	USA	131	22	NHL	Yes	Yes	114	4	Hospital-based control	No	2G ELISA
Shariff *et al.* (1999)	Canada	125	2	NHL	Yes	Yes	1085	11	Healthcare workers	No	3G EIA+RIBA
Paydas *et al.* (1999)	Italy	98	9	NHL	No	No	36,418	192	Blood donor control	No	3G ELISA
Vallisa *et al.* (1999)	Italy	175	65	B-cell NHL only	Yes	No	175	10	Hospital-based control	Age, sex	3G ELISA and RIBA
Pioltelli *et al.* (2000)	Italy	300	48	B-cell NHL only	Yes	No	600	51	Hospital-based control	No	3G ELISA and RIBA
Zucca *et al.* (2000)	Switzerland	180	17	B-cell NHL only	Yes	No	5424	49	Blood donor control	No	3G ELISA
Mizorogi *et al.* (2000)	Japan	125	17	NHL	Yes	Yes	452	18	Hospital-based control	No	2G EIA
Harakati *et al.* (2000)	Saudi Arabia	56	12	B-cell NHL only	Yes	No	104	3	Hospital-based control	No	2G EIA
Hausfater *et al.* (2001)	France	164	3	B-cell NHL only	Yes	No	694	3	Hospital-based control	No	3G ELISA
Kuniyoshi *et al.* (2001)	Japan	348	20	NHL	No	No	1,513,358	11,396	Blood donor control	No	3G ELISA
Montella *et al.* (2001)	Italy	111	28	NHL	Yes	Yes	226	17	Hospital-based control	No	3G ELISA
Rabkin *et al.* (2002)	USA	59	2	B-cell NHL only	Yes	No	95	0	Control drawn from same cohort	Age, sex	3G ELISA
Kaya *et al.* (2002)	Turkey	70	1	NHL	No	No	70	0	Healthy subjects	Age, sex	3G EIA
Imai *et al.* (2002)	Japan	187	23	NHL	Yes	Yes	197,600	10,176	Blood donor control	Age, sex	2G and 3G ELISA
Chindamo *et al.* (2002)	Brazil	109	10	NHL	Yes	Yes	39,371	472	Blood-donor-control	No	2G and 3G ELISA
Mele *et al.* (2003)	Italy	400	70	B-cell NHL only	Yes	No	396	22	Hospital-based control	No	3G EIA+RIBA
Avires *et al.* (2003)	Mexico	416	2	B-cell NHL only	Yes	No	832	1	Blood donor control	Age, sex	3G ELISA+RIBA
Iwata *et al.* (in press)	Japan	130	5	NHL	Yes	Yes	568	29	Hospital-based control	Age, sex	1G or 2G EIA

Abbreviations: ELISA, enzyme-linked-immunosorbent assay; EIA, enzyme-immunoassay; and RIBA, recombinant immunoblot assay. 2G and 3G stand for second generation and third generation, respectively.

Statistical analysis. We used odds ratio (OR) derived from variance-based methods as summary statistics for association. Heterogeneity among the studies was examined based on the method of DerSimonian and Laird by calculating the between-study variation (τ^2) from the Q statistic.[29] Weights for each study was given by taking inverse variance estimates of each study and τ^2 into consideration. Based on the significance in the Q statistics, we decided which model to use, a random-effect model or a fixed-effect model, in order to calculate summary OR and its 95% confidence interval (CI). Heterogeneity between studies was further evaluated by using meta-regression analysis.[30] In the univariate meta-regression analysis, the model examined number of anti-HCV tests applied to confirm HCV infection (1 or 2), use of matching in control selection (yes/no), hospital-based controls (yes/no), blood donor controls (yes/no), study from Italy (yes/no), study from Japan (yes/no), and published year of study. To evaluate possible publication bias, we used Begg's funnel plots and Begg's test.[31] In addition to overall analysis, subgroup analyses were planned in advance to evaluate the impact of HCV infection in 1) B-cell type NHL (B-NHL) subjects, 2) T-cell type NHL (T-NHL) subjects, 3) subjects in HCV-endemic countries (prevalence equal or higher than 2.5%, Brazil, Japan,[32] and Italy), 4) subjects in non-endemic countries (prevalence lower than 2.5%, Canada, France, Mexico, Saudi Arabia, Switzerland, Turkey, and the United States[32]), 5) studies using non-blood donor controls, and 6) studies using blood donor controls. Statistical significance was defined as a P value less than 0.05. We used the STATA statistical package (version 8, College Station, TX) for all analyses in this study.

Results

Description of studies. Characteristics of the studies are as shown in Table 1. Multiple studies were conducted in Italy (n=10), Japan (n=4), and the United States (n=2). The others consisted of single studies conducted in Brazil, Canada, France, Mexico, Saudi Arabia, Switzerland, and Turkey. Cases and controls ranged from 50 to 416 and 30 to 1,513,358 respectively. The total numbers of cases and controls in these studies were 4049 and 1,813,480. Eleven studies used hospital-based non-cancer controls, and six studies used blood donor control. In the study by Vallisa *et al*., only 175 inpatient non-cancer controls were included in the analysis.[28] Seven studies included blood donors as controls. Studies by Silvestri *et al*. and Mazzaro *et al*. used the same population-based control in a cohort[33] as a control group. A study by Rabkin *et al*. applied a Child Health and Development cohort for study.[24] Healthcare workers were used in the study by Shariff *et al*.[12] and healthy subjects from an unspecified population were applied in the study by Kaya *et al*.[23] Seven studies conducted matching for age in control selection, while the others did not. Information for B-NHL was available for 17 studies. Regarding anti-HCV antibody testing, 12 studies used a single test, while others used a combination of two tests. We performed tests for homogeneity using all subject studies and obtained a statistically significant result (Q=116.7 with degrees of freedom=22, P<0.001, τ^2=0.443) indicating the existence of between-study variability. Therefore, we decided to use a random-effect model to obtain summary statistics. The source of heterogeneity was explored by meta-regression analysis. The use of hospital-based controls, blood donor controls, and published year showed P values less than 0.15 (P=0.144 with a coefficient value of −0.47 for hospital-based controls, P=0.096 with coefficient 0.59 for blood donor controls, and P=0.086 with coefficient −0.11 for published year), indicating possible heterogeneity owing to these factors. Multivariate analysis indicated that blood donor usage in controls and year of publication are the statistically significant sources of heterogeneity (P=0.045 with coefficient 1.00 and P=0.019 with −0.16, respectively). Study in Italy, study in Japan, and use of matching in control selection all failed to show a significant result, indicating less influence of these factors on the overall result.

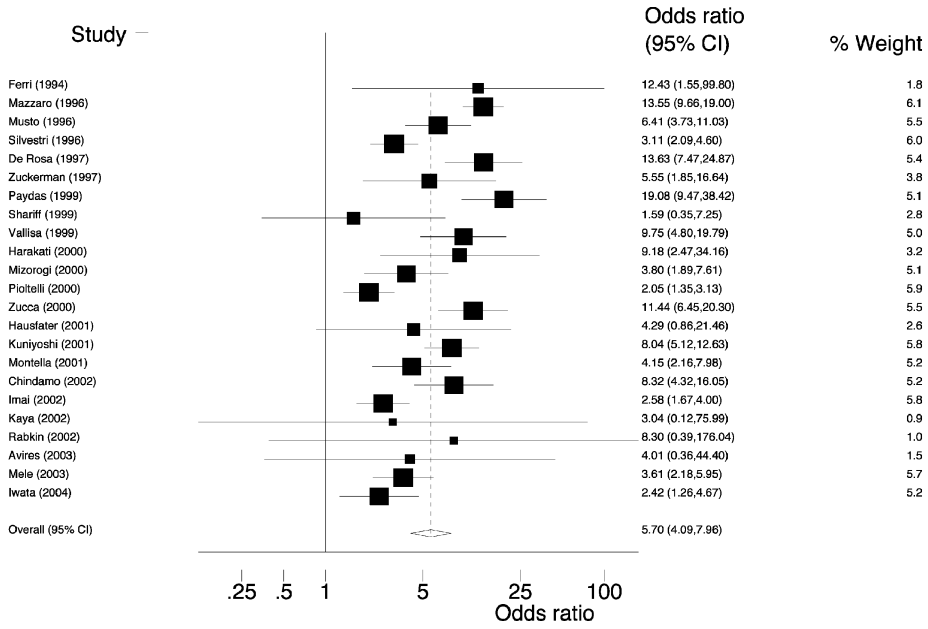

Fig. 1. The result of overall meta-analysis. The summary odds ratio (OR) and its 95% confidence interval (CI) are presented as an outlined diamond. The scale on the horizontal axis is logarithmic. The ORs and their 95% CIs are shown, along with weights in the calculation of summary OR. The result indicates that anti-HCV positive subjects have a 5.54 times higher risk for non-Hodgkin's lymphoma compared with anti-HCV negative subjects.

Meta-analysis. The results of overall analysis are summarized in Fig. 1. The summary OR for HCV-seropositive persons relative to negative persons is 5.70 (95% confidence interval (CI): 4.09–7.96, $P<0.001$). Begg's test did not support the existence of publication bias ($Z=0.30$, $P=0.763$). Additionally, a symmetrical distribution of studies in a funnel plot further suggests a lack of publication bias (Fig. 2). We further examined the association with only B-cell NHL as presented in Fig. 3(a). The OR was 5.04 (95% CI: 3.59–7.06) and this trend is similar to that of the overall analysis. As in the overall analysis, Begg's test and the funnel plot did not support the existence of publication bias. Nine studies could provide information for T-NHL analysis. In a meta-analysis for these studies, summary OR for T-NHL was 2.51 (95% CI: 1.39–4.56; Fig. 3(b)).

We further conducted a subgroup analysis according to the endemic status of countries. As shown in Fig. 4, consistent results were obtained in both endemic countries (OR=5.69, 95% CI: 3.85–8.42) and non-endemic countries (OR=7.14, 4.48–11.38). To explore possible selection bias of control, we further conducted a subgroup analysis according to usage of blood donor control. The ORs for non-blood-donor-control and blood-donor-control studies were 4.65 (3.10–6.97) and 8.43 (4.71–15.09), respectively.

Discussion

In this meta-analysis, we confirmed a strikingly positive association between anti-HCV positive status and risk of NHL, especially with B-NHL. Contrary to our expectation, endemic status of HCV did not change the significance of the association. In addition, we identified a possible selection bias owing to the use of blood donor controls.

Two possible biological mechanisms for lymphomagenesis, particularly for B-NHL, can be hypothesized (reviewed in reference 34)). The first is the direct phenotypical change of lymphocytes by HCV. Although a complete mechanism is not available for HCV-induced carcinogenesis of hepatocytes, viral replication in the cell is known to be important. E1/E2 envelope protein[35] or core protein[36] from the replicated virus induces transformation of hepatocytes. The same mechanism can be hypothesized for lymphomagenesis by HCV. HCV can be detected in B-lymphocytes, but evidence for HCV replication in lymphocytes is controversial. Therefore, the direct lymphomagenic effect of HCV is not clear at this point. A second possible mechanism is that HCV antigen stimulates the expansion of mono- or oligoclonal B-cells. Oligoclonal B-cell expansion in the peripheral blood was observed in 100% of HCV-infected patients with type II MC.[37] A similar phenomenon was reported for intrahepatic lymphocyte infiltrates of HCV-infected liver. Analysis of the Ig heavy/light chain usage revealed involvement of the specific V_H1-69 in patients with lymphoproliferative disorders.[38] Sequence analysis for these regions demonstrated somatic hypermutation, evidence for affinity mat-

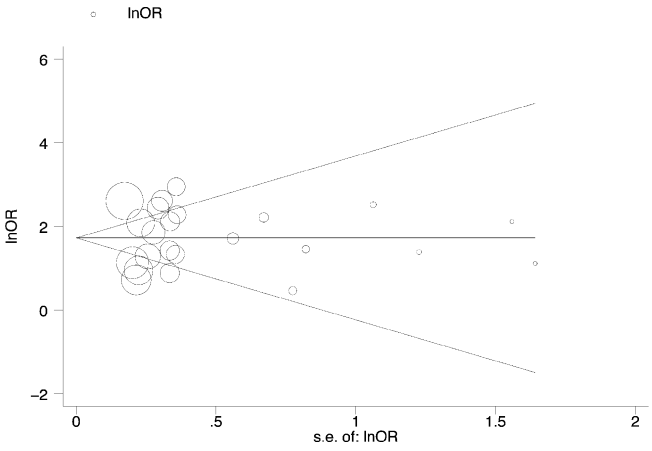

Fig. 2. Begg's funnel plot for publication bias in the overall analysis. Each circle indicates the odds ratio (OR) for non-Hodgkin's lymphoma comparing the anti-HCV negative subjects with the anti-HCV positive subjects, and the standard error of the natural logarithm of OR in each study. A vertically symmetrical distribution of circles indicates a substantial absence of publication bias.

uration under constant antigen stimulation.[38] Envelope protein E2 is now considered as a candidate antigen based on several lines of evidence: anti-HCV E2 B-cell clones from an HCV-infected patient preferentially used V_H1-69[39] and B-cell receptor from one HCV-associated lymphoma patient bound to E2.[40] CD81 is a cellular ligand for E2 envelope on the surface of lymphocytes.[41] CD19/CD21/CD81 complex along with B-cell receptor stimulation is considered to activate proliferation of lymphocytes.[42] The strong association we observed for B-NHL warrants further study regarding this issue. A similar CD81-E2 mediated mechanism is supported for T-cell NHL.[43] CD81-E2 cross-linking activates Lck through raft aggregation and thus leads to enhanced TCR signaling.[44] Although further clarification is required, the positive association we observed for T-NHL may be explained in part by this mechanism.

Possible limitations of our meta-analysis include heterogeneity between studies, meta-analysis of only case-control studies and possible publication bias. Regarding heterogeneity, we considered several factors in meta-regression analysis: matching, control selection, endemic status of HCV, and year of publication. Regarding the statistical model used to obtain the summary OR, we applied a random effect model to take between-study variation into consideration. This does not necessarily rule out the effect of heterogeneity between studies, but one may expect a very limited influence because of it. The significant associations detected were for the use of blood donor controls and year of publication. The use of blood donors in the study gave higher point estimates for OR and a more recent

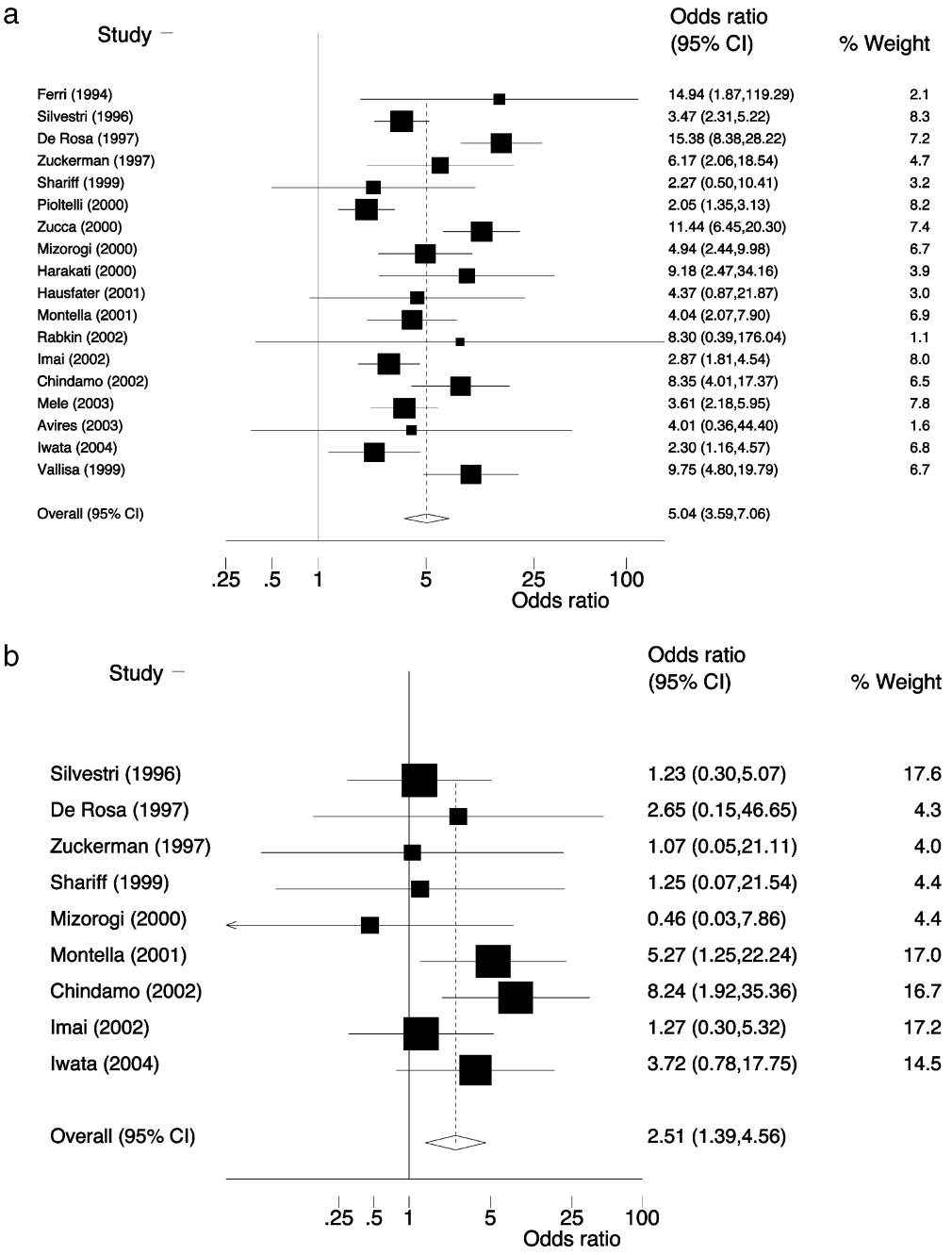

Fig. 3. The result of meta-analysis. Meta-analyses for B-NHL (a) and T-NHL (b) are presented. Both indicate a higher risk of NHL in anti-HCV positive subjects.

year of publication gave a lower OR. These results are intuitively understandable because, generally speaking, HCV screening in blood donation enhances the contrast between cases and controls and causal associations tend to be stronger in older reports than in recent ones. In addition, the significant OR even after exclusion of blood donor control studies indicates consistency across the studies and reliability of our meta-analysis even after the consideration of selection bias due to applying blood donor controls in the studies.[45] As age is an important risk factor for NHL, one would expect that age-matching in study design is essential. However, in our meta-regression analysis, its effect was revealed to be limited. Lack of matching risk factors for HCV infection, such as past history of blood transfusion, can be a cause of bias. We used only case-control studies and this might limit the ability to extrapolate our results. We identified only one cohort study regarding this topic. Ohsawa *et al*. conducted a retrospective cohort study but it did not have any HCV negative subjects within the cohort.[46] They used risk ratio (RR) calculated from ratio of expected incidence from a local cancer registry and observed incidence (4 cases out of 2162 subjects) as a substitute for measure of association (RR 2.10, 95% CI: 0.57–5.38). Although the RR is not significant,

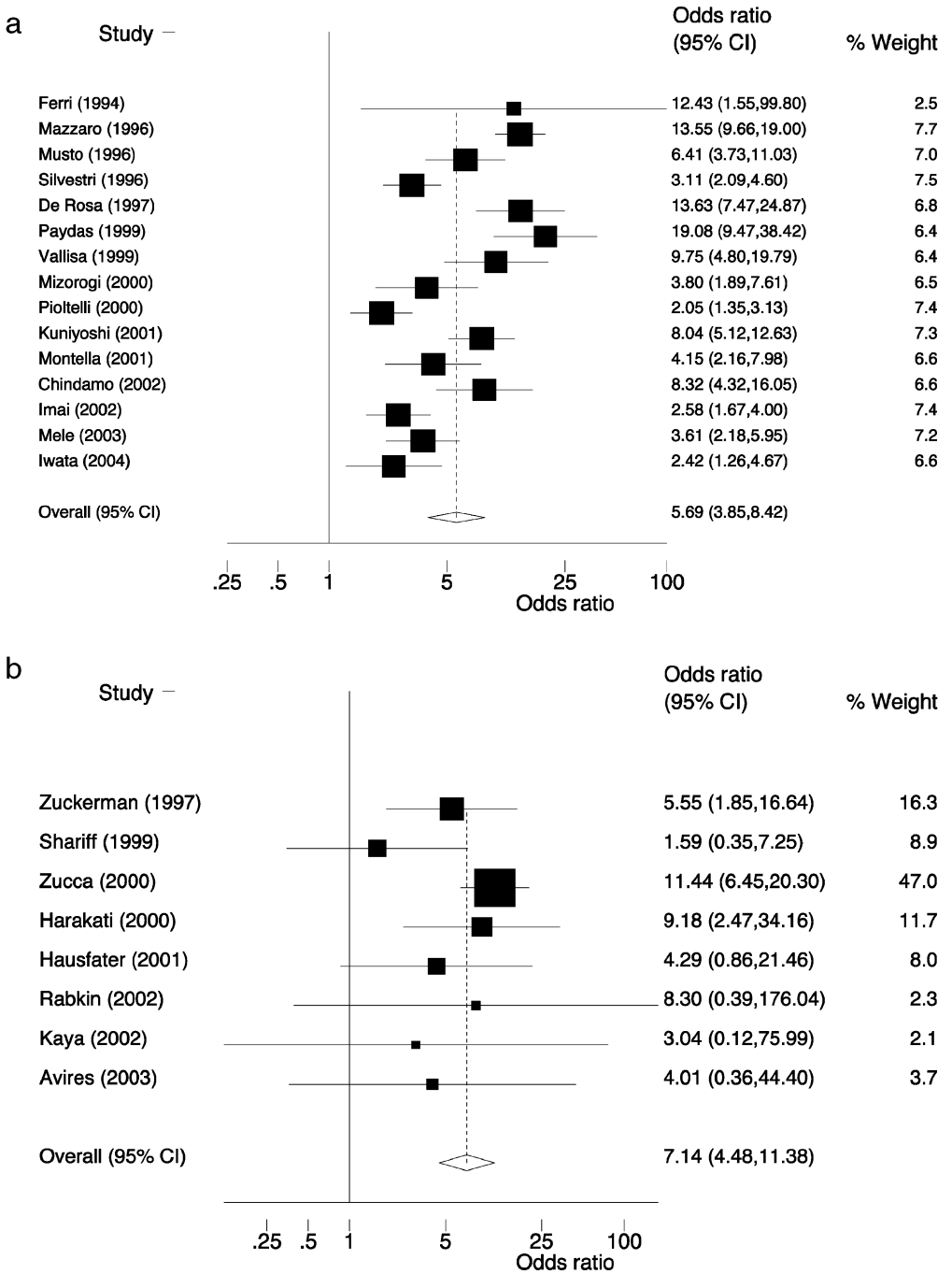

Fig. 4. The result of meta-analysis stratified by endemic status of the countries involved. (a) A meta-analysis of the studies conducted in endemic counties (Brazil, Italy, Japan, Mexico, and Saudi Arabia) is presented. (b) An analysis of the studies conducted in the non-endemic counties (Canada, France, Switzerland, Turkey, and the United States) is presented. Comparison of these results indicates that endemic status is not an effect modifier for the association between anti-HCV status and risk of non-Hodgkin's lymphoma.

the wide confidence interval indicates low statistical power for this association. Even when this RR was integrated into our analysis, the results were unchanged. We cannot completely rule out possible publication bias, as is often the case with meta-analysis, though statistical tests do not support its existence. Finally, the use of anti-HCV as a marker of HCV can be another limitation. Anti-HCV positivity is indicative both of active positivity and of past infection, while the presence of HCV RNA in serum is indicative of active viral replication. However, several studies in our analysis reported relatively good accordance between anti-HCV test and HCV-RNA test results.

The incidence of non-Hodgkin's lymphoma (NHL) is rapidly increasing throughout the world. It is notable that world standardized age-adjusted incidence rates of NHL in the United States for males and females between 1993 and 1997 are 16.4 (fifth most common) and 10.3 (sixth most common) per 100,000, respectively, based upon SEER data.[47] Therefore, the social burden of NHL has become increasingly important. On the other hand, the secular trend of HCV prevalence has not necessarily correlated with that of NHL, though the evidence regarding HCV prevalence is still insufficient in many countries.[48] This discrepancy is hard to interpret at this point, however we may speculate that factors, such as unknown infectious agents, which may negatively or positively interact with HCV may influence the lymphomagenicity. This issue should be considered in further epidemiologic studies.

Despite great efforts to uncover possible environmental risk factors for NHL, the current evidence is insufficient to aid in

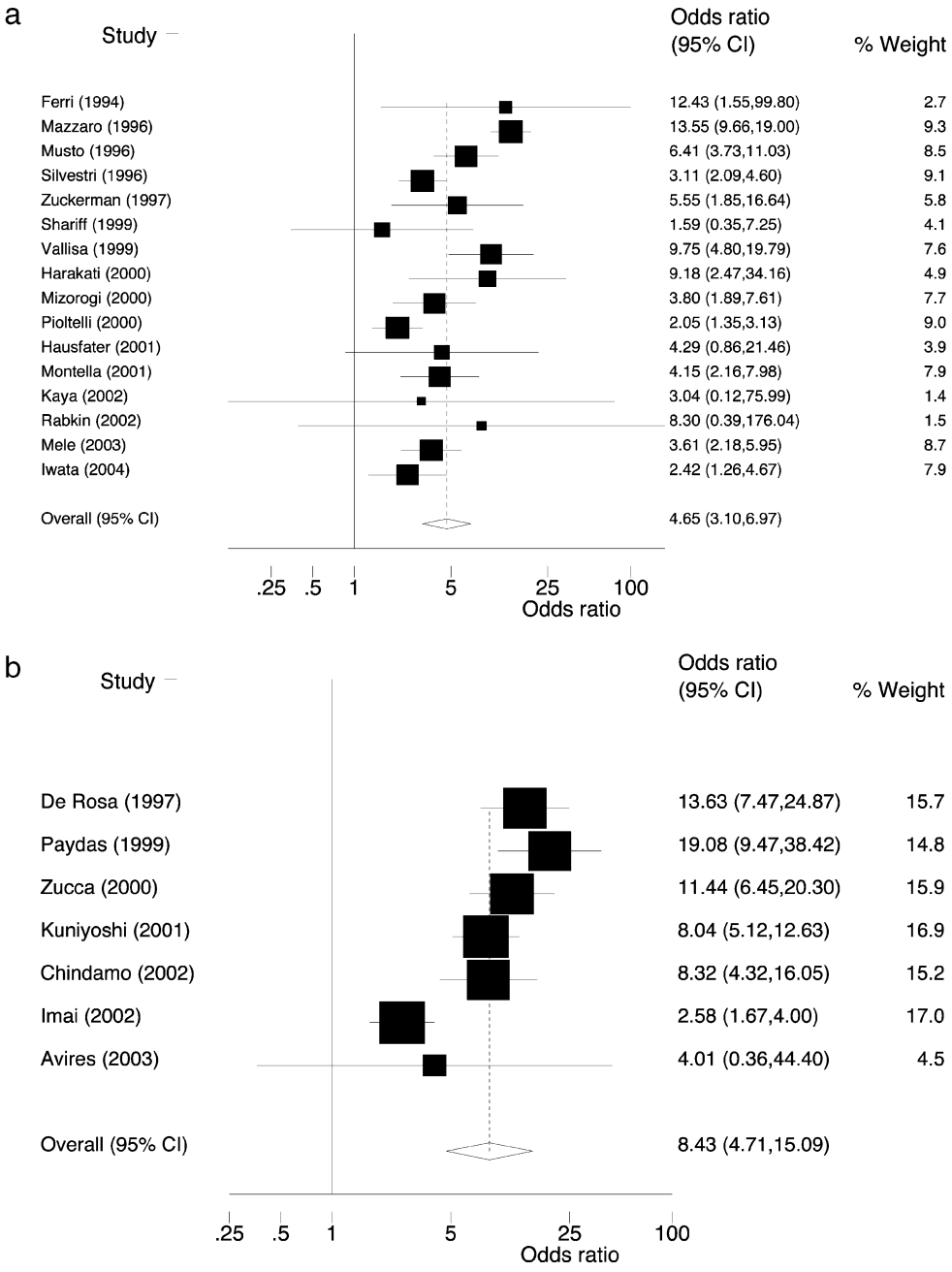

Fig. 5. The result of meta-analysis stratified by use of blood donor controls. (a) A meta-analysis of the studies in which non-blood donor controls were used is presented. (b) An analysis of the studies in which non-blood donor controls were used is presented. Results indicate an overestimation of the association in the studies using blood donor controls.

the prevention of NHL. Identification of infectious agents as risk factors for NHL has a great impact in terms of planning public health policies for prevention and development of new treatment. Excellent examples of this include HTLV-I for adult T-cell leukemia/lymphoma[49] and *Helicobacter pylori* for mucosa-associated lymphoid tissue lymphoma.[50] Although further biological evidence is needed, our findings strongly suggest that prevention of HCV infection can, at least to some extent, reduce NHL incidence in the future. Furthermore, as in the case report by Hermine *et al*.,[51] who reported regression of splenic marginal zone lymphoma after HCV treatment, one might expect HCV treatment itself to be an option for lymphoma treatment.

In conclusion, we confirmed that subjects with anti-HCV positive test have approximately five times higher risk of NHL. This association is consistent regardless of the endemic status of HCV, as well as subgroup analysis for B-/T-NHL. Further biological confirmation study is warranted.

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