Association of diabetes mellitus with non-Hodgkin lymphoma risk: a meta-analysis of cohort studies

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\textbf{ABSTRACT}

\textbf{Background:} Diabetes mellitus (DM) is considered to be a risk factor in the prognosis of many types of cancer, but the effect of DM on the risk of non-Hodgkin lymphoma (NHL) is still under dispute. We performed this study to examine the association between DM and subsequent NHL risk.

\textbf{Methods:} A systematically search had been performed in PubMed, Embase, and the Cochrane Library to identify eligible studies from inception to September 2018.

\textbf{Results:} Thirteen cohort studies were included, with a total of 902,4761 participants. The results showed that DM was associated with an increased risk of NHL (RR = 1.15, 95%CI: 1.02, 1.30, \(P = .03\)). Subgroup analyses suggested that DM was significantly associated with patients aged less than 60 years old (RR = 1.65, 95%CI: 1.31, 2.09, \(P < .0001\)), follow-up duration within 8 years (RR = 1.23, 95%CI: 1.02, 1.48, \(P = .03\)), and studies adjusted for body mass index (RR = 1.35, 95%CI: 1.01, 1.79, \(P = .04\)). The analyses within DM patients indicated that DM men were more likely to develop NHL than DM women (RR = 1.31, 95%CI: 1.04, 1.65, \(P = .02\)).

\textbf{Conclusions:} These results indicated that DM patients have significantly increased risk of NHL compared nondiabetics. Male DM patients were more likely to develop NHL compared with female. However, further large-scale studies are required to eliminate miscellaneous factors in all included studies.

Non-Hodgkin lymphoma (NHL) is a common malignancy of the hematopoietic system which is derived from lymphocytes. It was more common in developed countries, accounting for 4.3% of all cancers in the U.S.A. in 2014. Among all of common cancers, NHL ranked 7th in males, while 6th in females [1]. NHL has been increasing in Western countries over decades, especially in whites, men, and the elderly [2]. Although decades of efforts have been made to find out the pathophysiology of NHL, the causes of NHL remained unexplained [3].

Diabetes mellitus (DM) is a major global public health concern bothering approximately 3–4% of adults worldwide and contributing to around 1.3 million deaths worldwide. It is predicted to be among the five leading disease burden contributors by 2030 [4]. Prevalence of DM is a risk factor for various of diseases, including cardiovascular disease, kidney failure, dementia, and cancers at different sites, such as pancreas, colorectal, liver, lung, prostate, ovarian, breast, and endometrium [5–15]. Besides, according to a previous meta-analysis, DM patients had a greater potential to develop NHL [16]. However, in a recent study in Japan, DM was found increased risk of NHL in males, but not in females [17]. The object of this study was to perform a large-scale of available cohort studies to estimate the relationship between DM and NHL.

\textbf{Materials and methods}

\textbf{Literature search}

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement [18]. A systematic search of PubMed, Embase, and the Cochrane Library databases was performed from the first available date to 12 September 2018. For PubMed and Embase, the following key words were used: Medical Subject Heading (MeSH) or Emtree terms ‘diabetes’ or ‘diabetes mellitus’ or ‘metabolic syndrome’ or ‘obesity’ or ‘hyperglycemia’ or ‘fasting glucose’ and ‘lymphoma’ or ‘non-Hodgkin lymphoma’ or ‘non-Hodgkin’s lymphoma’ and ‘cohort’ combined with the corresponding free terms. Correlative keywords were used in the Cochrane Library. No language restrictions were applied to comprehensively search eligible articles.
**Inclusion and exclusion criteria**

Two reviewers independently selected eligible researches using the same criteria. Inclusion criteria included: (1) a cohort design; (2) assessment of NHL development with or without DM; (3) all NHLs were included, not just one, or several, subtypes; (4) reporting or providing sufficient information of odds ratios (ORs), hazard ratios (HRs), relative risks (RRs), and standard incidence ratios (SIRs); (5) patients over 18 years old. Exclusion criteria included: (1) a case report or cross-sectional design; (2) patients included have other diseases; (3) no available qualified data; (4) patients under 18 years old.

**Data extraction**

All data from publications were independently selected by two authors using the same criteria. The information extracted included: first author’s name, publication year, country, sample size, the age and generation, body mass index (BMI), numbers of NHL, follow-up duration, the outcome measured, and the adjustment factors. We tried our best to contact authors of original studies if there were missing data in the studies.

**Quality assessment**

Study quality was assessed independently by two authors using the Newcastle-Ottawa Scale (NOS) [19]. The NOS consists of three parameters of quality: 4 items for selection, 1 item for comparability, and 3 items for outcome. NOS scores of 1–3, 4–6, and 7–9 were assigned, respectively, for low, intermediate, and high-quality studies.

**Data synthesis and analysis**

Because the risk of NHL in the general population is very low, the RR was considered to approximate as OR, HR, and SIR [20]. Therefore, the primary outcome was measured as RR with 95% confidence interval (CI) of the relationship between DM and NHL.

**Statistical analysis**

In this meta-analysis, Reviewer Manager 5.3 was applied to analyze the data. The incidence of NHL in each literature was considered as a binary variable. A fixed or random-effect model was used to pool relative risk (RR) and 95% CI for effect estimated in each study [21]. Both Chi-square and I-square statistic were applied to analyze heterogeneity between studies. The heterogeneity was regarded significant when P-value < .1 [22] or I^2 > 50% [23]. Subgroup analyses were conducted for associations of country, mean age, follow-up, and the degree of adjustment, including BMI, smoking, and drinking. Sensitivity analyses were conducted by removing each individual study from the meta-analysis. Publication bias was assessed using Stata software (version 12.0). The Egger test [24] and Begg test [25] were used to assess publication bias. The P-value < .05 was viewed as statistical significance.

**Results**

**Study selection**

A comprehensively search was made for available eligible literatures. The process of the search was presented in Figure 1. A total of 468 articles met the criteria were selected after the initial search, of which 136 duplicates were discarded, 253 articles were excluded because of insufficient or irrelevant data. A total of 79 full-text records were selected. Thirty-six articles not reporting an effect estimate, 30 studies including duplicate participants were removed. Finally, only 13 articles were included into the meta-analyses [17,26–37].

**Study characteristics and quality assessment**

Baseline characteristics were summarized in Table 1. All of included studies had a cohort design. 9,024,761 participants were involved in 4 studies performed in U.S.A., 5 in European countries, and 4 in Asian countries. The follow-up duration ranged from 1 year to 35 years. The NOS was used to assess the quality of included articles. The score of 7 or greater was considered to be highly qualified.

**DM and NHL risk**

Due to significant heterogeneity (I^2 = 77%, P < .0001), a random-effect model was used to estimate pooled RR. The results showed that DM was associated with an increased risk of NHL (RR = 1.15, 95%CI: 1.02–1.30, P
Subsequently, we performed subgroup analysis according to country, mean age, follow-up, and the degree of adjustment, including BMI, smoking, and drinking. Subgroup analysis demonstrated that DM had significant effect on NHL in studies with patients mean age less than 60 years old (RR = 1.65, 95%CI = 1.31–2.09, P < .0001), follow-up duration within 8 years (RR = 1.23, 95%CI = 1.02–1.48, P = .03), and adjusting for BMI (RR = 1.35, 95%CI = 1.01–1.79, P = .04) (Figure 2).

### DM and NHL risk in men and women

A total of seven cohort studies assessed the incidence rate of NHL in DM patients between men and women. Pooled analysis demonstrated that significant differences existed between men and women (RR = 1.31, 95%CI = 1.04–1.65, P = .02) (Figure 3). DM men were more likely to develop NHL than DM women. Though there existed moderate heterogeneity (P = .02, I² = 61%).

### DM and NHL risk in different subtypes

As shown in Table 3, only 2 articles have investigated the association between DM and NHL risk in various subtypes [27,28]. Since the available data are limited, more studies are needed to explore the effects of DM on different NHL subtypes.

#### Publication bias

Both Egger test (P = .210) and Begg test (P = .096) showed no significant evidence of publication bias.

Figure 2. Association between diabetes mellitus and the risk of non-Hodgkin lymphoma.
Moreover, the funnel plots seemed symmetric (Figure 4), which also indicated no publication bias.

**Discussion**

This meta-analysis was an update of the association between DM and NHL. The results showed that the diabetic group may have mild-to-moderate increased odds of developing NHL compared with those without diabetes, which was consistent with a previous meta-analysis [16]. The subgroup analysis indicated that these association might be different according to mean age at baseline, follow-up duration, and adjustment for BMI. A former study suggested that BMI was positively related to NHL and mortality, which was consistent with the subgroup analyses [38]. Furthermore, an analysis about the incidence rate of NHL was performed between diabetic men and women. The results demonstrated that diabetic men were more likely to develop NHL than women with diabetes.

Both sensitivity and subgroup analyses were used to explore the source of heterogeneity. Sensitivity analyses were performed by removing each research from the meta-analysis to see if the research might influence the heterogeneity. The results showed that no significant changes have been found when excluded each research, though moderate heterogeneity might still exist.

Previous meta-analyses combined case–control and cohort studies in order to explore the association of DM with NHL risk [16]. Although the study showed similar results with ours, lack of subgroup analyses weakened its liability. Furthermore, the study failed to show the heterogeneity results, which might affect the accuracy of the conclusion. In addition, the differences between males and females were not performed.

Nowadays, a growing body of evidence indicated that DM was associated with the risk of NHL. Yang et al analyzed the association between diabetes and the risk of NHL using data from the Shanghai Men’s

### Table 2. Subgroup analysis of relative risk for the association between DM NHL risk.

| Subgroup                  | No. of references | RR and 95% CI       | P value | I²%  | P-value for heterogeneity |
|---------------------------|-------------------|---------------------|---------|------|--------------------------|
| Country                   |                   |                     |         |      |                          |
| Western countries         | 8                 | 1.09 (0.97–1.22)    | 0.13    | 53   | .04                      |
| Eastern countries         | 2                 | 1.39 (0.61–4.12)    | 0.34    | 96   | .00001                   |
| Mean age at baseline      |                   |                     |         |      |                          |
| ≤60                       | 3                 | 1.65 (1.31–2.09)    | <0.0001 | 87   | .005                     |
| >60                       | 5                 | 1.04 (0.99–1.10)    | 0.10    | 62   | .03                      |
| Follow-up duration        |                   |                     |         |      |                          |
| ≤58                       | 5                 | 1.23 (1.02–1.48)    | 0.03    | 87   | <0.0001                  |
| >58                       | 5                 | 1.10 (0.96–1.27)    | 0.18    | 19   | .29                      |
| Adjusted BMI              |                   |                     |         |      |                          |
| Yes                       | 4                 | 1.35 (1.01–1.79)    | 0.04    | 85   | .0001                    |
| No                        | 4                 | 1.01 (0.96–1.06)    | 0.77    | 0%   | .65                      |
| Adjusted smoking          |                   |                     |         |      |                          |
| Yes                       | 2                 | 1.84 (0.94–3.63)    | 0.08    | 87   | .005                     |
| No                        | 6                 | 1.02 (0.98–1.07)    | 0.32    | 0    | .50                      |
| Adjusted drinking         |                   |                     |         |      |                          |
| Yes                       | 3                 | 1.49 (0.90–2.47)    | 0.12    | 90   | <0.0001                  |
| No                        | 5                 | 1.02 (0.97–1.08)    | 0.37    | 8    | .36                      |

**Table 3.** Relative risk for subtypes of NHL according to studies.

| References                | NHL subtypes | B-NHL subtypes |
|---------------------------|--------------|----------------|
|                           | T-NHL        | B-NHL          | DLBCL | FL | CLL/SLL |
| Khan, 2008, men [27]      | 0.77 (0.10–5.76) | 1.37 (0.94–1.99) | 1.70 (0.67–4.3) | 1.52 (0.46–5.0) | 2.0 (1.04–3.86) |
| Khan, 2008, women [27]    | 0.72 (0.41–1.29) | 1.46 (0.60–3.36) | 0.74 (0.18–3.0) | 1.07 (0.33–3.43) |
| Erber, 2009 [28]          | 0.87 (0.62–1.21) | 1.03 (0.59–1.81) | 0.85 (0.52–1.38) |

Note: T-NHL: T-cell NHL; B-NHL: B-cell NHL; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; CLL/SLL: chronic lymphocytic leukemia/small-cell lymphocytic lymphoma.
The present study also had certain limitations. First, the present meta-analysis did not distinguish T1DM from T2DM because few researches had done so. Due to combining the two types of DM, the relation between DM and NHL risk might be somehow influenced. However, since the most common form of DM was T2DM, particularly among older patients, it is likely that the majority of participants in this article were T2DM. Second, the miscellaneous factor could involve in the studies. Some studies adjusted age, sex, physical activity, education, lifestyle, and many other related factors, while others adjusted fewer factors. These literatures controlled some variables, however, there was still no uniform rule for exclusion factors. Third, case–control studies and individual cases were not involved in this meta-analysis, which precluded a more detailed analysis for comprehensive results. Fourthly, since the available data are limited, more studies are needed to investigate the association between DM and NHL risk in various subtypes.

Conclusion

In summary, this study suggested that DM had a potentially harmful impact on NHL risk. Physicians and health professionals should focus on DM treatment in NHL patients combined with DM, instead of merely cancer treatment.

Acknowledgements

This work was supported by “215” high-level health technology talents training plan (No.2015-3-006).

Disclosure statement

No potential conflict of interest was reported by the authors.

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