The association between type 1 and 2 diabetes mellitus and the risk of leukemia: a systematic review and meta-analysis of 18 cohort studies

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Abstract. Diabetes mellitus (DM) is widely considered to be associated with the risk of diverse cancers; however, the association between DM and the risk of leukemia is still controversial. Thus, a detailed meta-analysis of cohort studies was conducted to elucidate this association. Eligible studies were screened through the electronic searches in PubMed, Web of Science, and Embase from their inception to August 11, 2020. Summary relative risks (RRs) and 95% confidence intervals (CIs) were computed through the random-effects model. Eighteen articles involving 10,516 leukemia cases among a total of 4,094,235 diabetic patients were included in this meta-analysis. Overall, twenty-five RRs were synthesized for type 2 diabetes mellitus (T2DM) and yielded a summary RR of 1.33 (95%CI, 1.21–1.47; p < 0.001). For type 1 diabetes mellitus (T1DM), 7 RRs were combined, however, the pooled RR was insignificant (RR, 1.08; 95%CI, 0.87–1.34; p = 0.48). Interestingly, the summary RR for East Asia (RR, 1.83, 95%CI, 1.63–2.06) was significantly higher than that for Europe (RR, 1.11, 95%CI, 1.06–1.15), Western Asia (RR, 1.40, 95%CI, 1.25–1.54), North America (RR, 1.14, 95%CI, 1.08–1.20), and Australia (RR, 1.47, 95%CI, 1.25–1.71). Moreover, we found that patients with a shorter T2DM duration (1–5 years) had a higher risk of leukemia compared to those with a longer duration (5.1–10 years). Overall, this meta-analysis suggests there is a moderately increased risk of leukemia among T2DM patients, but not in T1DM patients. Further investigation is warranted.

Key words: Leukemia, Type 2 diabetes mellitus, Type 1 diabetes mellitus, Risk, Meta-analysis

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LEUKEMIA is a cluster of life-threatening haematopoietic cancers [1], characterized by abnormal proliferation and development of white blood cells and their precursors [2]. Leukemia was reported to be the 15th and 11th most common cause of cancer occurrence and death worldwide, respectively, with an estimated 437,033 new leukemia cases and 309,006 leukemia deaths in 2018 [3].

The global upsurge in the incidence of diabetes mellitus (DM) has become one of the largest challenges to public health in the 21st century [4]. As documented in the International Diabetes Federation (IDF) Diabetes Atlas 2017, 425 million individuals aged between 20 to 79 years suffered from diabetes in 2017, which increased by 10 million compared with 2015 [5]. Moreover, diabetes has been reported as a predisposing factor for the onset of diverse cancers, including the liver, bladder, colorectal, breast, ovarian, endometrial and non-Hodgkin’s lymphoma [6-9].

The risk of leukemia among diabetic patients has been explored by some epidemiological studies, but the results were inconsistent. A meta-analysis of 11 observational studies in 2012 revealed a 22% increased risk of leukemia in patients suffering from type 2 diabetes mellitus (T2DM) as compared to the euglycemic population [10]. However, the association between T1DM and leukemia risk remains ambiguous. A number of new cohort studies investigated the association between T2DM and leukemia [11-21]. Therefore, we conducted an updated meta-analysis of cohort studies to provide a more accurate estimate of the association between diabetes and the risk of development of leukemia.

Methods

Search strategy and selection criteria

To identify eligible studies investigating the association...
between diabetes and risk of leukemia, two researchers (YPF and WYB) independently conducted the literature search in PubMed, Web of Science, and Embase from their inception to August 11, 2020. The following search key terms were used in combination: “diabetes mellitus”, “DM”, “leukemia”, “leukaemia”, “cohort”, “follow-up”, “prospective” and “longitudinal” (Supplementary Table 1). The reference lists of previously published systematic reviews were also examined to find additional published articles.

We included studies that met the following selection criteria: 1) the study was cohort design; 2) the association between diabetes mellitus (type 1 diabetes mellitus (T1DM) or T2DM) and leukemia risk was reported; 3) the study reported the effect sizes (ESs) (standard incidence ratio (SIR), relative risk (RR), or hazard ratio (HR)) and their corresponding 95% confidence intervals (CIs). If there were multiple published papers from the same population or cohort, priority was given to the study with the longest follow-up time. Studies in which gestational diabetes was the exposure of interest were excluded. The researchers scanned the titles and abstracts to exclude the irrelevant articles, and the eligibility of the remaining studies were determined by reading the full text.

**Data extraction and quality assessment**

The baseline characteristics of each included study was extracted independently by two reviewers (YPF and WYB): the first author’s last name, year of publication, country, duration of follow-up, participant characteristics (number of cases, sex, age range or mean age at entry), source of control group (population-based or hospital-based), number of leukemia cases, identification of DM and leukemia, RRs with their 95% CIs, and adjusted confounders in the analysis. When studies reported several multivariate adjusted effect estimates, we extracted the RRs with the greatest control for confounders. Two reviewers (YPF and WYB) checked each other’s data after the extraction process and disagreements were addressed by discussion with the third investigator (ZJJ).

Two researchers (YPF and WYB) independently assessed the quality of the included studies based on the Newcastle-Ottawa scale (NOS) [22]. There were 3 parameters to assess cohort studies: selection (4 points), comparability (2 points) and outcome assessment (3 points). Studies scoring 7–9 points were considered to be of high quality, studies scoring 4–6 points were defined as moderate quality, and 0–3 as low quality.

**Statistical analysis**

Summary relative risks (RRs) and corresponding 95% CIs were calculated to explore the association between DM and leukemia risk through random effects model [23]. We synthesized RRs according to different subtype (T1DM and T2DM) of DM respectively. Since T2DM accounted for the vast majority of diabetes worldwide (about 90%), studies that did not distinguish diabetes subtypes and only reported RRs for the pooled diabetes in adults were assigned to the T2DM group. We used the Cochran $Q$ and $I^2$ statistics to evaluate statistical heterogeneity among included studies. A $p$ value of $<0.10$ or an $I^2$ statistic of $\geq 50\%$ is considered to represent substantial heterogeneity among studies.

Subgroup and sensitivity analyses were conducted for all included studies and studies which focused on T2DM. Subgroup and meta-regression analyses were stratified by effect estimate (RR&HR, and SIR), gender (males and females), study location (Europe, Western Asia, East Asia, North America, and Australia), control population (DM-free as control and population as control), the number of cases ($\leq 100$, $>100$), follow-up time ($<10$ years, and $\geq 10$ years), T2DM measured by robust methods (hospital diagnosis, medication use, and database records), NOS score ($<7$ and $\geq 7$), and adjustments of potential confounding factors, such as alcohol use, smoking, BMI/obesity, race/ethnicity and socioeconomic status (Yes vs. No). For sensitivity analyses, we excluded one study at a time and recalculated the summary RRs to assess whether the single study had a significant effect on the overall estimate. However, we did not conduct these analyses for studies investigating T1DM because of the limited number of studies.

We used funnel plots to assess publication bias. Furthermore, Egger’s linear regression tests were conducted and a $p$ value of $<0.10$ indicated potential publication bias. All statistical analyses were performed using Stata, version 14.0 (Stata Corp, College Station, Texas).

**Results**

Online searching retrieved a total of 1,466 relevant articles originally, whereas 15 additional studies were retrieved through reference searches. The meta-analysis finally incorporated a total of 18 eligible articles [11-21, 24-30], one of which was obtained by manually searching the reference list of relevant literature [26]. The identification process of relevant studies was illustrated in Fig. 1.

**Characteristics in included studies**

The baseline characteristics of the eligible studies are displayed in Supplementary Table 2. We included 22 cohort studies involving 10,516 leukemia cases among a total of 4,094,235 diabetic patients (the study of Carstensen et al. [16] included five cohorts). The publication year of these articles ranged from 1982 to 2019. Of these 18 articles,
16 focused on both types of DM or specifically investigated T2DM [11-15, 17-21, 24-27, 29, 30], while T1DM was exclusively explored in only 5 of these articles [14, 16, 25, 27, 28]. The studies were conducted in the following countries: UK (n = 4) [16, 19, 27, 30], the United States (n = 3) [12, 24, 29], China (n = 3) [11, 13, 20], Sweden (n = 3) [15, 16, 28], Finland (n = 2) [16, 21], Australia (n = 2) [14, 16], Denmark (n = 2) [16, 25], South Korea (n = 1) [26], Italy (n = 1) [18], Israel (n = 1) [17].

Among these 18 studies, 10 studies [11, 13-15, 18, 20, 21, 25, 27, 28] applied SIR to identify the association between DM and risk of leukemia, while the remaining 8 studies [12, 16, 17, 19, 24, 26, 29, 30] adopted incidence rate (RR or HR). Fifteen studies were retrospective cohort studies based on registry-data [11, 13-21, 25, 27-30] and 3 were prospective cohort studies [12, 24, 26]. Besides, out of 18 studies, 13 were population-based [11-14, 16-18, 21, 24-28] and 5 studies [15, 19, 20, 29, 30] were based on hospital. Furthermore, hospital diagnostic records and cancer registry data were utilized in all these studies to ascertain leukemia cases, which was reliable and robust compared to the self-report methods.
1.54; $I^2 = 0.0\%$), North America (RR, 1.14; 95%CI, 1.08–1.20; $I^2 = 0.0\%$) and Australia (RR, 1.47, 95%CI, 1.25–1.71; $I^2 = 66.2\%$). According to the univariate meta-analysis, the primary source of variability between studies was the study location ($I^2$-squared res = 2.16%; Adjusted $R^2$ = 97.80%). Moreover, the studies that adjusted for BMI/obesity (RR, 1.13, 95%CI, 1.07–1.19; $I^2 = 0.0\%$) were also found to have lower risk of leukemia with T2DM compared with those that did not (RR, 1.42, 95%CI, 1.26–1.60; $I^2 = 91.1\%$).

In addition, when excluded one study at a time and recalculate the pooled RRs, the results did not appreciably change and the estimates in each case were well within the confidence limits of the overall estimate (Supplementary Fig. 1).

**T2DM duration and leukemia risk**

The effect of T2DM duration on the risk of leukemia was elucidated in only 5 of the 18 included studies. As illustrated in Table 2, the highest risk of leukemia occurrence was discovered in patients within one year of T2DM diagnosis (RR, 3.48; 95%CI, 1.75–6.94; $p < 0.001$). The positive association was also obtained in the 1–5 years group (RR, 1.17; 95%CI, 1.04–1.33; $p = 0.012$) and 5.1–10 years group (RR, 1.10; 95%CI, 1.01–1.20; $p = 0.029$). However, when T2DM was diagnosed ≥10 years, the pooled RR reduced to 1.03 (95%CI, 0.90–1.19; $p = 0.644$).

**Publication bias**

The funnel plot for meta-analysis could not rule out potential publication bias (Supplementary Fig. 2). The Egger’s test of all included risk estimates showed no
Table 1  The results of subgroup analyses for association between T2DM and leukemia

| Subgroup                  | Number of studies | RR (95%CI)       | Test(s) of heterogeneity | p values for meta-regression |
|---------------------------|-------------------|------------------|--------------------------|-----------------------------|
|                           |                   |                  | Q            | p         | I^2     |                             |                             |
| Effect size               |                   |                  |              |           |         |                             |                             |
| SIR                       | 9                 | 1.47 (1.25–1.71) | 207.88        | <0.001    | 94.7%   | 0.089                        |
| RR&HR                     | 7                 | 1.22 (1.12–1.33) | 19.96         | 0.068     | 39.9%   |                             |
| Gender                    |                   |                  |              |           |         |                             |                             |
| Male                      | 10                | 1.35 (1.15–1.59) | 148.61        | <0.001    | 93.3%   | 0.821                        |
| Female                    | 8                 | 1.41 (1.07–1.87) | 154.22        | <0.001    | 94.8%   |                             |
| Study location            |                   |                  |              |           |         |                             |                             |
| East Asia                 | 4                 | 1.83 (1.63–2.06) | 12.77         | 0.026     | 60.9%   | 0.001                        |
| Europe                    | 7                 | 1.11 (1.06–1.15) | 3.31          | 0.973     | 0.0%    | 0.002                        |
| North America             | 3                 | 1.14 (1.08–1.20) | 1.37          | 0.712     | 0.0%    | 0.008                        |
| Australia                 | 1                 | 1.47 (1.25–1.71) | 2.96          | 0.085     | 66.2%   | 0.631                        |
| Western Asia              | 1                 | 1.40 (1.25–1.54) | 0.02          | 0.892     | 0.0%    |                             |
| Control population        |                   |                  |              |           |         |                             |                             |
| DM-free as control        | 6                 | 1.29 (1.10–1.50) | 110.57        | <0.001    | 90.1%   | 0.572                        |
| Population as control     | 10                | 1.36 (1.20–1.55) | 163.40        | <0.001    | 93.9%   |                             |
| Number of leukemia        |                   |                  |              |           |         |                             |                             |
| ≤100                      | 8                 | 1.26 (1.08–1.46) | 19.53         | 0.021     | 53.9%   | 0.523                        |
| >100                      | 8                 | 1.37 (1.20–1.56) | 206.64        | <0.001    | 94.70%  |                             |
| Follow-up time            |                   |                  |              |           |         |                             |                             |
| <10                       | 4                 | 1.59 (1.07–2.37) | 33.2          | <0.001    | 84.9%   | 0.337                        |
| ≥10                       | 12                | 1.30 (1.18–1.44) | 188.7         | <0.001    | 90.5%   |                             |
| T2DM measured by robust methods |        |                  |              |           |         |                             |                             |
| Yes                       | 9                 | 1.44 (1.25–1.67) | 204.28        | <0.001    | 94.1%   | 0.094                        |
| No                        | 7                 | 1.19 (1.10–1.29) | 15.07         | 0.179     | 27.0%   |                             |
| NOS score                 |                   |                  |              |           |         |                             |                             |
| <7                        | 9                 | 1.47 (1.23–1.75) | 99.47         | 0         | 89.9%   | 0.196                        |
| ≥7                        | 7                 | 1.26 (1.10–1.43) | 132.97        | 0         | 90.2%   |                             |
| Adjusted for alcohol use  |                   |                  |              |           |         |                             |                             |
| Yes                       | 4                 | 1.15 (1.03–1.29) | 7.97          | 0.158     | 37.2%   | 0.110                        |
| No                        | 12                | 1.41 (1.24–1.59) | 211.13        | <0.001    | 91.5%   |                             |
| Adjusted for smoking      |                   |                  |              |           |         |                             |                             |
| Yes                       | 3                 | 1.16 (0.97–1.39) | 7.86          | 0.097     | 49.1%   | 0.194                        |
| No                        | 13                | 1.38 (1.24–1.55) | 230.24        | <0.001    | 91.7%   |                             |
| Adjusted for BMI/obesity  |                   |                  |              |           |         |                             |                             |
| Yes                       | 3                 | 1.13 (1.07–1.19) | 1.59          | 0.811     | 0.0%    | 0.035                        |
| No                        | 13                | 1.42 (1.26–1.60) | 213.35        | 0         | 91.1%   |                             |
| Adjusted for race/ethnicity |               |                  |              |           |         |                             |                             |
| Yes                       | 2                 | 1.29 (1.10–1.50) | 10.85         | 0.004     | 81.6%   | 0.825                        |
| No                        | 14                | 1.34 (1.19–1.51) | 220.69        | <0.001    | 90.5%   |                             |
| Adjusted for socioeconomic status |         |                  |              |           |         |                             |                             |
| Yes                       | 2                 | 1.29 (1.12–1.49) | 8.87          | 0.012     | 77.5%   | 0.847                        |
| No                        | 14                | 1.34 (1.19–1.51) | 228.6         | <0.001    | 90.8%   |                             |

Table 2  Summary RRs for the association between T2DM and leukemia according to diabetes duration

| Diabetes duration, years | References | Number of RR | RR (95%CI) | p     |
|-------------------------|------------|--------------|------------|-------|
| <1                      | [15, 17]   | 3            | 3.48 (1.75–6.94) | <0.001 |
| 1–5                     | [17, 30]   | 2            | 1.17 (1.04–1.13) | 0.012  |
| 5.1–10                  | [17, 30]   | 2            | 1.10 (1.01–1.20) | 0.029  |
| ≥10                     | [17, 30]   | 2            | 1.03 (0.90–1.19) | 0.644  |
| >1                      | [14, 15, 19, 28, 30] | 7        | 1.40 (1.16–1.70) | 0.001  |
| >2                      | [14, 15, 17, 30] | 9        | 1.18 (1.07–1.30) | 0.001  |
Discussion

Evaluating the 18 articles, including 22 cohort studies, a 33% elevated risk of leukemia was found to be associated with T2DM. However, this significantly positive association was not witnessed in T1DM. According to the subgroup analyses, both male and female T2DM patients developed an elevated risk of leukemia as compared to the general population or with those without DM. Furthermore, the risk of leukemia appeared to be inversely associated with the duration of T2DM, which may be related to the treatment of diabetes. When T2DM was diagnosed over 10 years, there was no significant difference in the risk of leukemia in diabetics compared to the general population. Although some variations were marked in the pooled RRs of sensitivity analyses, all of them had point estimates greater than 1 and most of the corresponding CIs overlapped with that of the summary RR in overall meta-analysis. These findings presumed a robust positive association.

In the subgroup analysis of T2DM, compared with the western countries, East Asia portrayed a more substantial association between T2DM and leukemia. Differential genetic background and environmental factors, such as the country-specific dietary patterns, may justify this outcome. Higher levels of trans-fat and saturated fat prevailing the western dietary pattern [31] may promote cancer development [32, 33]. A multicenter case-control study in China reported that elevated risk of leukemia was correlated with dietary intake of animal fat and dietary habits with frequent intakes of fat, deep-fried, and smoked foods (p for trend < 0.05) [34]. Moreover, Solans et al. estimated the association between overall diet and chronic lymphocytic leukemia (CLL), and found that high adherence to a western dietary pattern (i.e., high intake of high-fat dairy products, processed meat, refined grains, sweets, caloric drinks, and convenience food) was associated with CLL (OR, 1.19; 95%CI, 1.03–1.37) [35]. Notably, dietary pattern is a stable eating habit formed over a long period and hyperglycemia always exists before T2DM diagnosis. Therefore, in the case that individuals with hyperglycemia caused by the long-term high-fat diet were assigned to the control population, T2DM can only display a relatively weak impact on leukemia development.

The studies that adjusted for BMI/obesity were appeared to have a lower risk of leukemia with T2DM compared with those that did not. The association between BMI and the onset of leukemia is convincing. A meta-analysis including 65 different studies documented that the risk of leukemia, including acute, chronic myeloid lymphoma (AML and CML), and CLL, was aggravated with BMI (RR, 1.09; 95%CI, 1.03–1.15) [36]. However, only three of the included studies adjusted for BMI/obesity and these three studies controlled for many confounders. Therefore, it was difficult to reliably determine whether variation in relative risk was due to differences in obesity adjustment or other factors.

In our meta-analysis, we also investigated the impact of diabetes duration on the leukemia risk. The first year of follow-up estimated 3.48 folds risk of leukemia in T2DM than among the euglycemic population. The incidence of leukemia was also significantly increased in patients suffering from T2DM for 1–5 years and 5.1–10 years. However, the risk of leukemia declined to the level of the general population among patients with T2DM diagnosed for ≥10 years. Detection bias and reverse causality may account for the highest risk for leukemia observed in the first year following the diagnosis of diabetes. Leukemia cases identified due to increased screening or physical examination after diabetes diagnosis may be affected by detection bias. Besides, undiagnosed leukemia could indulge in insulin sensitivity and trigger various biological pathways to suppress insulin secretion [37], which may lead to diabetes. The risk of leukemia appears to be inversely associated with diabetes duration. Certain cancers, such as pancreatic cancer [38], non-Hodgkin’s lymphoma [6], exhibit a similar association with T2DM, though the mechanism has not yet been established. However, it should be noted that there are a limited number of studies investigating the effect of T2DM duration on the incidence of leukemia, and thus we can not rule out the possibility that this result was just accidental. The treatment of diabetes may be responsible for the inverse association between T2DM duration and leukemia incidence, if real. The hypoglycemic drugs reduce the fasting serum glucose of diabetic patients and maintain it at a normal level. This, in turn, forbids the development of hyperglycemia-induced leukemia.

We found no significant association between T1DM and leukemia risk. Acute lymphocytic leukemia (ALL) and T1DM is reported to share an environmental etiology and common epidemiological features [39], including similar age distributions and correlated international incidence, which suggested a significant positive correlation between them (r = 0.53). However, in another study, Feltbower et al. scrutinized the association between the two diseases within small areas in a region in the north of the United Kingdom and only reported a correlation coefficient of 0.33. Furthermore, after controlling the deprivation index, the correlation coefficient dropped to a negligible level (r = 0.06) [40]. Based on population-based registries, Richiardi et al. also analyzed the
incidence of the two diseases and opined that their incidence was not correlated in the same birth cohorts ($r = -0.34$; $p = 0.41$) [41]. These findings support our results that T1DM was not associated with increased incidence of leukemia.

The pathophysiological mechanism behind the diabetes-induced increased leukemia risk remains unknown. Based on the following facts, we speculated that hyperglycemia might play a crucial role in the relationship between T2DM and leukemia risk. First, elevated fasting serum glucose levels have been identified as an independent risk factor for certain cancers, and the risk enhances with rising glucose levels [42]. Second, adequate research has substantiated the fact that hyperglycemia can trigger DNA damage and then cause DNA mutation, which may be responsible for the development of leukemia [43]. Third, some studies have also documented that the response to glucose process is associated with CML [44, 45].

Several strengths of the present study are detailed as follows. First, the available evidence was gathered and summarized from the cohort studies that dealt with the impact of DM on leukemia risk. The large sample size of our study was powerful enough to estimate the association between DM and the risk of leukemia. Second, the recall bias in case-control studies could be avoided as our meta-analysis concentrated only cohort studies. Third, this is the first meta-analysis that investigated the association between T1DM and leukemia risk. Finally, although with limited data, we also explored the effect of T2DM’s duration upon leukemia risk.

Limitations of our study should also be acknowledged. First, the association between T2DM and leukemia risk may be modified by confounders. We observed that the pooled RRs for studies that adjusted for alcohol use, smoking, and BMI/obesity was somewhat weaker than those that did not. Additionally, most of the included studies used registry-based data, and details on some important potential confounders, such as a family history of hematological malignancies, obesity status, career, and exposure to benzene and radioactive materials, were not available. Therefore, the role of these confounders in the association between T2DM and leukemia risk remains imprecise. Second, recent research has highlighted the inverse association of some antidiabetic drugs, such as metformin, with the risk of certain cancers [46-49]. Unfortunately, the role of these drugs in the relationship between DM and leukemia risk has rarely been elucidated in the included studies. Finally, different leukemia subtypes have varied epidemiological patterns and risk factors. Thus, in-depth research is essential to determine the differences in the impact of T2DM on the risk of different leukemia subtypes.

**Conclusion**

The results of this meta-analysis indicate that T2DM is associated with an elevated risk of leukemia in both men and women. Future studies should differentiate between the different leukemia subtypes and explore their risk in persons with T2DM. The role of potential confounders in the association between T2DM and leukemia risk, such as BMI, family history of leukemia and drug use, also requires more well-designed studies to clarify.

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**Ethical Approval**

For this type of study (i.e. retrospective), formal consent is not required.

**Research Involving Human Participants and/or Animals**

This article does not contain any studies with human or animal subjects performed by any of the authors.

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