Meta-Analysis

Type 2 Diabetes Mellitus and Risk of Non-Hodgkin Lymphoma: A Systematic Review and Meta-Analysis

Chun Chao¹ and John H. Page²

¹ Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA.
² Department of Epidemiology, Harvard School of Public Health, Boston, MA.

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Type 2 diabetes mellitus is associated with altered immune function and chronic inflammation. Both of these immune conditions are implicated in the pathogenesis of non-Hodgkin lymphoma. The authors performed a systematic review to summarize findings from the current literature on the association between history of type 2 diabetes mellitus and risk of non-Hodgkin lymphoma. Ten case-control studies and three prospective cohort studies were included in this review. Meta-analysis found that a history of type 2 diabetes mellitus was positively associated with overall non-Hodgkin lymphoma risk. However, there was significant heterogeneity between studies. Study design was an important source of heterogeneity. The rate ratio between type 2 diabetes mellitus and non-Hodgkin lymphoma was found to be 1.18 (95% confidence interval: 0.99, 1.42) among case-control studies and 1.79 (95% confidence interval: 1.30, 2.47) among the prospective cohort studies. Weaknesses were identified in some of the included studies in the areas of case and control selection, measurement of covariates and non-Hodgkin lymphoma, and confounding control. Although a positive association between type 2 diabetes mellitus and risk of non-Hodgkin lymphoma was suggested, the evidence is inconclusive because of methodological limitations of the included case-control studies. More prospective studies with improved control of confounding are needed to confirm these findings.

diabetes mellitus; diabetes mellitus, type 2; lymphoma; lymphoma, non-Hodgkin; meta-analysis

Abbreviations: CI, confidence interval; RR, rate ratio; TNF-α, tumor necrosis factor-α.

Non-Hodgkin lymphoma is the fifth leading cause of incident cancer in both men and women in the United States (1). The incidence of non-Hodgkin lymphoma has been rising globally since the 1970s (2), although the reason for this increase is unclear. Medical conditions characterized by chronic inflammation, such as systemic lupus erythematosus and rheumatoid arthritis, are associated with excess risk of non-Hodgkin lymphoma (3). Chronic inflammation may promote lymphogenesis through the effects of proinflammatory cytokines on lymphocyte proliferation and survival. Several metabolic disorders, such as obesity and type 2 diabetes mellitus, are also known to be associated with a low-grade, systemic, proinflammatory state. As the growing prevalence of type 2 diabetes mellitus parallels the rise in non-Hodgkin lymphoma incidence, it has been postulated that these metabolic disorders may be contributing to non-Hodgkin lymphoma etiology.

Type 2 diabetes mellitus is a condition characterized by insulin resistance and pancreatic ß-cell dysfunction. There is an established link between insulin resistance and inflammation. Although proinflammatory factors, such as tumor necrosis factor-α (TNF-α), promote insulin resistance (4, 5), insulin also acts as a mediator for the inflammatory response (6, 7). Insulin attenuates the up-regulation of hepatic acute-phase protein gene expression induced by inflammatory cytokines (6). Studies show that insulin might regulate the
synthesis of cortisol binding globulin (7), a liver protein that is closely involved in inflammatory events. Several recent human and animal studies provide further evidence of the antiinflammatory action of insulin (8–12). Therefore, impaired insulin action may have implications for lymphogenesis. Reports of excess non-Hodgkin lymphoma risk among diabetic patients date back to two decades ago (13). In recent years, the number of studies that have examined the relation between type 2 diabetes mellitus and malignancy has surged because of an increased interest in hypotheses linking hyperinsulinemia to malignancy. However, findings on diabetes and non-Hodgkin lymphoma have been inconsistent. As the incidences of type 2 diabetes mellitus and non-Hodgkin lymphoma continue to rise, the association between type 2 diabetes mellitus and non-Hodgkin lymphoma warrants closer examination. We conducted a systematic review of published epidemiologic studies that evaluated the relation between type 2 diabetes mellitus and non-Hodgkin lymphoma case ascertainment, proportion of cases histologically confirmed, adjusted odds/rate ratio estimates, 95 percent confidence intervals, adjusted odds/rate ratio estimates and confidence intervals by non-Hodgkin lymphoma subtypes, and adjustment factors. Two researchers (C. C., J. H. P.) independently performed data extraction. Discrepancies were resolved by consensus.

**MATERIALS AND METHODS**

**Study identification**

We first conducted a database search to identify epidemiologic studies examining the association between any type of diabetes mellitus (type 1 or type 2 or in combination) and cancer or lymphoma risk. Studies published before November 2007 were identified by searching the PubMed and EMBASE databases using the following keywords in the title/abstract text: diabetes (title/abstract), diabetic (title/abstract), medical history (title/abstract), medical conditions, cancer (title), malignancy (title), and lymphoma (title/abstract). We then reviewed the references cited by each article identified from the database search for additional articles.

**Inclusion/exclusion criteria**

Studies that examined the association between type 2 diabetes mellitus or all diabetes mellitus and risk of non-Hodgkin lymphoma were included in this review. We excluded studies that focused on the examination of type 1 diabetes or that did not specifically examine the outcome of non-Hodgkin lymphoma (e.g., did not distinguish non-Hodgkin lymphoma from Hodgkin’s lymphoma). Studies that did not have individual-level data or an internal comparison group were not considered for this analysis. Studies that did not provide an appropriate measure of precision (e.g., 95 percent confidence intervals, standard error, or p value) were also excluded. Because diabetes may affect non-Hodgkin lymphoma survival, we also excluded studies that used non-Hodgkin lymphoma mortality as the outcome. Where there was overlap in the study populations of published papers, the largest of the studies was included, and the others excluded.

**Data extraction**

For each study, the following information was extracted when possible and applicable: publication date, type of study (prospective vs. retrospective cohort and case-control studies), country where the study was conducted, study period, age, gender and ethnicity of the subjects, source of cases (in case-control studies), method of control selection (in case-control studies), response rate, matching, ascertainment of diabetes mellitus, methods for non-Hodgkin lymphoma case ascertainment, proportion of cases histologically confirmed, adjusted odds/rate ratio estimates, 95 percent confidence intervals, adjusted odds/rate ratio estimates and confidence intervals by non-Hodgkin lymphoma subtypes, and adjustment factors. Two researchers (C. C., J. H. P.) independently performed data extraction. Discrepancies were resolved by consensus.

**Study evaluation**

The methodological quality of each case-control study was evaluated by systematically reviewing the following factors: case representativeness (source of cases and response rate), the extent to which controls were a random sample of the population that the cases arose from and response rate, measurement procedures for covariates and outcome, attempts to minimize temporal ambiguity, measured confounders, and the extent to which these were controlled for (e.g., linear, categorical (number of categories), or regression smoothing). For cohort studies, the methods for statistical analysis and case ascertainment were also considered.

**Data analysis**

We conducted a meta-analysis to summarize findings from the current literature. Summary rate ratio estimates were calculated for all studies combined, as well as by subgroup. We performed analyses stratified by study design (case-control and prospective cohort), source of controls, gender, region where the study was conducted, and whether the study indicated the adjustment for body mass index/obesity. Odds ratio estimates from case-control studies and one cohort study were used to approximate the non-Hodgkin lymphoma rate ratio, the latter approximation made on the basis that non-Hodgkin lymphoma is rare. Several studies (14–19) did not report an overall effect estimate for diabetes on non-Hodgkin lymphoma and provided only subgroup-specific estimates. For these studies, an inverse variance-weighted mean of the subgroup-specific log-odds ratio or log-rate ratio estimates was used in the overall meta-analyses.

The random effects model of DerSimonian and Laird (20) was used to calculate the summary log-rate ratio, by using the study-specific estimates of log-rate ratio and their respective standard errors, with the “meta” command in STATA, version 9, software (21). Heterogeneity between studies was examined by using the Mantel-Haenszel test for heterogeneity. A p value of less than 0.10 was used as an indication of the presence of heterogeneity. Meta-regression (22) was used to explore factors affecting the rate ratio estimates. We examined female gender, region where the study was conducted, and adjustment for body mass index as potential explanatory variables for heterogeneity between studies, while adjusting for study design (prospective cohort vs. case-control). For influence analysis, studies...
were excluded one at a time to determine their magnitude of influence on the overall summary estimate. We consider a study influential if the exclusion of it changed our conclusion or the effect estimate by at least 20 percent. Publication bias was assessed by the regression asymmetry test of Egger et al. (23) (p < 0.10 as an indication for publication bias) and by visual inspection of Begg’s funnel plot.

RESULTS

We identified a total of 31 epidemiologic studies that examined the association between history of diabetes and lymphoma. Among them, 18 were excluded from this review (15, 19, 24–39). Figure 1 shows the list of excluded studies and the reasons for exclusion. A total of 10 published case-control studies met the inclusion criteria (13, 16, 40–46). Of these, five were conducted in the United States or Canada, four were conducted in Europe, and one was conducted in Taiwan. Characteristics of the included case-control studies are summarized in table 1. Zahm et al. (46) reported results from two independent US-based case-control studies; one was a case-control study from Kansas (47), and the other was conducted in Iowa and Minnesota (48). The 10 case-control studies included a combined total of 6,079 cases and 81,908 controls.

In terms of case selection, Lin et al. (42) included only non-Hodgkin lymphoma cases referred for radiation therapy. Cerhan et al. (40), Holly and Bracci (41), and Cartwright et al. (13) had a case-response rate of less than 80 percent and might have primarily included cases that were alive and well enough to be interviewed (the less severe cases). Fortuny et al. (16) did not report the case-response rate. In terms of control selection, four studies appeared to have had a well-defined source population (41, 42, 47, 48). These studies identified cases from state cancer registries (with one exception (41)) and sampled controls from statewide random digit dialing and Medicare files. The source population was poorly defined in the report by Lin et al. (42), in which cases were those referred to the study center. There were three hospital-based studies (13, 16, 43). It was not stated whether incident non-Hodgkin lymphoma diagnosed during a diabetes-related admission was excluded from the case sample in these three studies. Further, Cartwright et al. (13) did not provide details for the selection of their inpatient controls. The control response rate was lower than 80 percent in several population-based studies (40, 41, 43, 48). Fortuny et al. (16) and Cartwright et al. (13) did not report the control response rate. Only four studies clearly indicated the exclusion of human immunodeficiency virus-positive subjects (16, 40–42).

We identified a total of three published prospective cohort studies and no retrospective cohort study that reported the association between diabetes and incident non-Hodgkin lymphoma (14, 17, 18). Of these, one was conducted in the United States, and two were conducted in Japan. The characteristics of these cohort studies are summarized in table 2. The study by Kuriki et al. (18) studied a hospital outpatient clinic-based cohort, whereas the other two were

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**FIGURE 1.** List of excluded studies. NHL, non-Hodgkin lymphoma.
### TABLE 1. Summary of case-control studies of history of type 2 diabetes mellitus and risk of non-Hodgkin lymphoma

<table>
<thead>
<tr>
<th>First author, year (reference)</th>
<th>Country</th>
<th>Gender</th>
<th>Case source (response rate)</th>
<th>Real case sample</th>
<th>No. of cases</th>
<th>Control source (response rate)</th>
<th>No. of controls</th>
<th>Diabetes ascertainment (diabetes mellitus type)</th>
<th>Adjustment factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin, 2007 (42)</td>
<td>Taiwan</td>
<td>Men and women</td>
<td>Historical cohort of cases referred to the radiation-oncology department (100%)</td>
<td>Radiation therapy cases</td>
<td>242</td>
<td>Population-based multiple screening program (100%)</td>
<td>71,379</td>
<td>Self-report (not specified)</td>
<td>Age, gender, hypertension, smoking, alcohol drinking, betel nut use</td>
</tr>
<tr>
<td>Scotti, 2007 (44)</td>
<td>Italy</td>
<td>Men and women</td>
<td>Incident non-Hodgkin lymphoma cases admitted to study hospitals (95%)</td>
<td>Hospitalized incident cases</td>
<td>671</td>
<td>Hospital controls admitted for acute conditions (e.g., trauma, orthopedic, surgical, and other miscellaneous illness) (95%)</td>
<td>1,799</td>
<td>Self-report (not specified)</td>
<td>Age, gender, education, residence, study center</td>
</tr>
<tr>
<td>Rousseau, 2006 (43)</td>
<td>Canada</td>
<td>Men</td>
<td>Cases ascertained from the major hospitals in Montreal (82%)</td>
<td>No details described</td>
<td>195</td>
<td>Population controls sampled from electoral lists (72%)</td>
<td>509</td>
<td>Self-report (not specified)</td>
<td>Age, ethnicity, education, family income, proxy status, body mass index, farming</td>
</tr>
<tr>
<td>Fortuny, 2005 (16)</td>
<td>Spain</td>
<td>Men and women</td>
<td>All consecutive cases having diagnosis of lymphoma at four study centers (response rate not reported)</td>
<td>No details described</td>
<td>292</td>
<td>Hospital controls admitted for conditions other than cancer, transplant, and systemic infection; exclusions admitted for diabetes-related complications (response rate not reported)</td>
<td>595</td>
<td>Self-report (type 2*)</td>
<td>Age, gender, center, socioeconomic status, body mass index</td>
</tr>
<tr>
<td>Cerhan, 2005 (40)</td>
<td>United States</td>
<td>Men and women</td>
<td>Incident cases from four SEER† regions identified by rapid reporting system (78%)</td>
<td>Alive, located, giving consent, and well enough to be interviewed</td>
<td>759</td>
<td>Population controls sampled from the four SEER regions by random digit dialing and from Medicare/Medicaid files (44%)</td>
<td>589</td>
<td>Self-report (type 2*)</td>
<td>Age, gender, ethnicity, study center</td>
</tr>
<tr>
<td>Holly, 2003 (41)</td>
<td>United States</td>
<td>Men and women</td>
<td>Cases residing in six counties in the San Francisco Bay area identified by rapid case-finding system (56%)</td>
<td>Alive, located, giving consent, and well enough to be interviewed</td>
<td>1,304</td>
<td>Population controls sampled by random digit dialing and from Medicare files (78%)</td>
<td>2,402</td>
<td>Self-report (not specified)</td>
<td>Age, gender</td>
</tr>
<tr>
<td>Vineis, 2000 (45)</td>
<td>Italy</td>
<td>Men and women</td>
<td>Cases from the study centers identified via periodical surveys in the hospital departments (100%)</td>
<td>All incident cases</td>
<td>1,388</td>
<td>Population controls residing in the hospital serving areas sampled by demographic or National Health Service files (81%)</td>
<td>1,718</td>
<td>Self-report (not specified)</td>
<td>Age, gender; explored social class, education, and study center as potential confounders</td>
</tr>
<tr>
<td>Zahn, 1995 (46)</td>
<td>United States</td>
<td>Men (Kansas)</td>
<td>Incident cases identified from Kansas cancer registry; included deceased cases (86%)</td>
<td>Located and giving consent</td>
<td>169</td>
<td>Population controls sampled by random digit dialing and from Medicare or state mortality files (93%)</td>
<td>948</td>
<td>Self-report (not specified)</td>
<td>Age, race (White only), vital status</td>
</tr>
<tr>
<td>Zahn, 1995 (46)</td>
<td>United States</td>
<td>Men (Iowa and Minnesota)</td>
<td>Incident cases identified from Iowa State Health Registry and a special surveillance of Minnesota hospital and pathology laboratory records; included deceased cases (89%)</td>
<td>Located and giving consent</td>
<td>622</td>
<td>Population controls sampled by random digit dialing and from Medicare files or state death certificates (77%)</td>
<td>1,245</td>
<td>Self-report (not specified)</td>
<td>Age, race (White only)</td>
</tr>
<tr>
<td>Cartwright, 1988 (13)</td>
<td>Scotland</td>
<td>Men and women</td>
<td>Cases identified from hospitals in Yorkshire and regional cancer registry; excluded diffuse, lymphocytic, and well-differentiated lymphomas (31%)</td>
<td>Alive, untreated, giving consent, and well enough to be interviewed</td>
<td>437</td>
<td>Hospital controls admitted for a wide variety of nonmalignant conditions; details not provided (response rate not reported)</td>
<td>724</td>
<td>Self-report (not specified)</td>
<td>Age, gender, residence</td>
</tr>
</tbody>
</table>

* Type 2 defined as diagnosed or onset after age 30 years.
† SEER, Surveillance, Epidemiology, and End Results.
TABLE 2. Summary of cohort studies of history of type 2 diabetes mellitus and risk of non-Hodgkin lymphoma

<table>
<thead>
<tr>
<th>First author, year (reference)</th>
<th>Country</th>
<th>Cohort</th>
<th>Case identification</th>
<th>No. of non-Hodgkin lymphoma cases</th>
<th>Diabetes ascertainment (type)</th>
<th>Adjustment factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuriki, 2007 (18)</td>
<td>Japan</td>
<td>Hospital-based Epidemiologic Research Program at Aichi Cancer Center: 19,540 men and 39,900 women</td>
<td>Hospital- and population-based cancer registries</td>
<td>Men, 194; women, 148</td>
<td>Self-report (both types)</td>
<td>Age, body mass index, alcohol drinking, smoking, physical activity, bowel movement, family history of non-Hodgkin lymphoma, family history of diabetes, dietary restriction, raw vegetable intake, greasy food intake, snacking</td>
</tr>
<tr>
<td>Khan, 2006 (17)</td>
<td>Japan</td>
<td>Japan Collaborative Cohort Study: 23,378 men and 33,503 women</td>
<td>Municipal cancer registries</td>
<td>Men, 27; women, 17</td>
<td>Self-report (not specified)</td>
<td>Age, body mass index, smoking, alcohol drinking</td>
</tr>
<tr>
<td>Cerhan, 1997 (14)</td>
<td>United States</td>
<td>Iowa Women’s Health Study: 37,934 women</td>
<td>Iowa State Cancer Registry</td>
<td>114</td>
<td>Self-report (type 2*)</td>
<td>Age, marital status, farm residence, history of blood transfusion; explored obesity, body fat distribution, diet, family history of cancer as potential confounder</td>
</tr>
</tbody>
</table>

* Type 2 defined as diagnosed after age 30 years.

In this systematic review, the included studies suggest that there is a positive relation between history of type 2 diabetes mellitus and risk of non-Hodgkin lymphoma. Both Khan et al. (17) and Cerhan et al. (14) utilized analytical techniques that used survival time. Kuriki et al. (18) used logistic regression that analyzed cumulative incidence and retrospectively excluded all non–non-Hodgkin lymphoma cancers from the study sample. These studies included a total of 500 non-Hodgkin lymphoma cases arising from 154,255 participants. Incident cases in all studies (including case-control studies) were either based on cancer registries or were 100 percent historically confirmed.

Results from the meta-analysis for all studies combined and by subgroup are presented in table 3. The meta-analysis for all studies showed a positive association between history of diabetes and non-Hodgkin lymphoma (rate ratio (RR) = 1.28, 95 percent confidence interval (CI): 1.07, 1.53) (figure 2). In subgroup analysis by study design, a statistically significant positive association was observed in hospital-based case-control studies and cohort studies, but not in population-based case-control studies. From the studies that evaluated subgroups by gender, a positive association was also found among women. A statistically significant elevated rate of non-Hodgkin lymphoma for persons with diabetes was observed among studies conducted in Europe (RR = 1.23, 95 percent confidence interval: 0.99, 1.52) and East Asia (RR = 1.74, 95 percent confidence interval: 1.31, 2.33), but not among studies conducted in North America (RR = 1.11, 95 percent confidence interval: 0.82, 1.50). Meta-analysis for studies adjusting for body mass index showed a statistically significant positive association between type 2 diabetes mellitus and non-Hodgkin lymphoma (RR = 1.56, 95 percent confidence interval: 1.23, 2.00).

There was statistically significant heterogeneity of the results of the included studies (p = 0.05). Meta-regression suggested that study design was a significant predictor for heterogeneity. None of geographic location, adjustment for body mass index, or gender was a significant predictor for heterogeneity in the meta-regression after adjusting for study design. In influence analysis, no study was found to be particularly influential, relative to the others. Egger’s test did not indicate the presence of publication bias. We also did not find clear evidence of publication bias from inspecting the funnel plot (figure 3).

DISCUSSION

In this systematic review, the included studies suggest that there is a positive relation between history of type 2 diabetes mellitus and risk of non-Hodgkin lymphoma by subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of studies</th>
<th>Rate ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>13</td>
<td>1.28</td>
<td>1.07, 1.53*</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case-control</td>
<td>10</td>
<td>1.18</td>
<td>0.99, 1.42</td>
</tr>
<tr>
<td>Hospital based</td>
<td>3</td>
<td>1.36</td>
<td>1.00, 1.86</td>
</tr>
<tr>
<td>Population based</td>
<td>7</td>
<td>1.12</td>
<td>0.89, 1.40</td>
</tr>
<tr>
<td>Prospective cohort</td>
<td>3</td>
<td>1.79</td>
<td>1.30, 2.47</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>7</td>
<td>1.15</td>
<td>0.84, 1.59</td>
</tr>
<tr>
<td>Women</td>
<td>5</td>
<td>1.60</td>
<td>1.15, 2.22</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>6</td>
<td>1.11</td>
<td>0.82, 1.50</td>
</tr>
<tr>
<td>Europe</td>
<td>4</td>
<td>1.23</td>
<td>0.99, 1.52</td>
</tr>
<tr>
<td>East Asia</td>
<td>3</td>
<td>1.74</td>
<td>1.31, 2.33</td>
</tr>
<tr>
<td>Adjustment for body mass index</td>
<td></td>
<td>8 1.16 0.93, 1.45</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>1.56</td>
<td>1.23, 2.00</td>
</tr>
</tbody>
</table>

* For all studies: χ² heterogeneity = 0.05; Egger’s test: p = 0.51.
diabetes mellitus and subsequent risk of non-Hodgkin lymphoma. Evidence that this is so is that the included prospective cohort studies found an increased rate ratio (summary RR = 1.79, 95 percent confidence interval: 1.30, 2.47). However, we identified a number of methodological limitations in the literature, which is cause for question of the unbiasedness of the summary estimate.

We identified several limitations in the literature in the areas of study design, covariate and outcome measurement, and confounding control. Most of the studies included in this review were case-control studies, which are more susceptible to a number of biases relative to cohort studies. Several studies collected only non-Hodgkin lymphoma cases who were well enough to be interviewed. In these studies, a significant portion of the identified cases (15–30 percent) were not interviewed because of disease progression (deceased or too ill) (13, 40, 41). This could introduce bias if type 2 diabetes mellitus is a determinant of non-Hodgkin lymphoma severity. Two of the evaluated studies included deceased cases and controls and interviewed next of kin to avoid selection bias associated with non-Hodgkin lymphoma progression (47, 48). Although use of next of kin may sometimes introduce measurement error, this design feature may be desirable when rapid case ascertainment is not feasible. Overall, we did not identify a significant problem related to the planning of control selection in the population-based case-control studies, except for that by Lin et al. (42). However, the lower response rate in the population controls, on average, may be a significant source of selection bias.

Both cohort and case-control studies are subject to bias when there is differential non-Hodgkin lymphoma detection. This is particularly a concern for indolent lymphomas that are either asymptomatic or present with few symptoms. Individuals with diabetes are exposed to the health-care system more frequently than are nondiseased nondiabetics (49, 50) and, thus, may be more likely to be diagnosed with lymphoma. However, none of the epidemiologic studies included in this review included a procedure for ruling out non-Hodgkin lymphoma from the “noncases.” This is less likely to be a significant problem in hospital-based case-control studies, because of the facts that non-Hodgkin lymphoma is relatively rare and that hospital-based controls are also exposed to the health-delivery system. Prospective studies based on cohorts with successive physical examinations may be the best design to address this detection bias issue. On the other hand, underdiagnosis of diabetes may be common (51) and can be an important concern in both case-control and cohort studies. Furthermore, differential bias can be induced when the diagnosis of diabetes is prompted by the diagnosis of non-Hodgkin lymphoma. This can be addressed by considering the exposure as type 2 diabetes mellitus only when it is
clearly diagnosed prior to the onset of non-Hodgkin lymphoma. However, besides the prospective studies, only three of the case-control studies restricted the exposure variable to diabetes diagnosed at least 1 year prior to the non-Hodgkin lymphoma diagnosis (16, 41, 42).

History of diabetes was ascertained by self-report in all the evaluated studies. A previous study found that self-report for diabetes had high specificity (>99 percent) but low sensitivity (66 percent) (52). The Charlson comorbidity index was also negatively associated with diabetes self-report (52). These findings suggest that population-based case-control studies may be especially susceptible to differential misclassification of diabetes status. Most studies also did not collect information to distinguish type 1 from type 2 diabetes mellitus. Type 1 diabetes is etiologically different from type 2 diabetes. Although we intended to study the effect of type 2 diabetes mellitus on the risk of non-Hodgkin lymphoma, we included studies that combined both types of diabetes. However, we do not expect the mixture of these two conditions to have significantly affected our findings, as type 1 diabetes generally accounts for a small proportion of prevalent diabetes (53).

Another area of weakness of the studies that evaluated the type 2 diabetes mellitus–non-Hodgkin lymphoma relation is that many did not adequately control for confounding. Type 2 diabetes mellitus and non-Hodgkin lymphoma may have common causes such as age, adiposity, lifestyle factors, correlates of socioeconomic status, and certain medical conditions. A positive association between obesity and non-Hodgkin lymphoma has been suggested (54). Two recent meta-analyses, one based on 13,289 non-Hodgkin lymphoma cases from prospective studies (55) and the other based on 16 studies (10 cohorts and six case-controls) with a total of 21,720 cases (56), reported significantly elevated non-Hodgkin lymphoma risk with increased body mass index. Larsson and Wolk (56) further reported that the positive association for obesity was found only for diffuse large B-cell lymphoma but not for follicular lymphoma or small lymphocytic/chronic lymphocytic leukemia. Another meta-analysis based on 18 case-control studies with a total of 10,453 cases did not find an association between overweight/obesity and risk of non-Hodgkin lymphoma, except a significantly elevated risk for diffuse large B-cell lymphoma among severely obese individuals (body mass index: ≥40 kg/m²) (57). As obesity is among the most important risk factors for type 2 diabetes mellitus, fully adjusting for the effect of measures such as body mass index is important for causal inference. There were several studies that adjusted for only basic demographic variables, and few provided adequate control for body mass index and socioeconomic status. In the present study, summary estimates from studies adjusting for body mass index suggested an elevated non-Hodgkin lymphoma risk among persons with diabetes. However, most of these studies modeled body mass index as two or three categories, leaving the possibility for residual confounding. Use of methods such as regression smoothing to improve confounder control has still not become a common feature of epidemiologic studies.

Findings from some studies suggest that disease characteristics of diabetes may be potential effect modifiers.

### TABLE 4. Odds ratios reported by non-Hodgkin lymphoma subtype

<table>
<thead>
<tr>
<th>First author, year (reference)</th>
<th>Odds ratio (95% confidence interval)</th>
<th>Odds ratio (95% confidence interval)</th>
<th>Odds ratio (95% confidence interval)</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin, 2007 (42)</td>
<td>1.61 (0.94, 2.77)</td>
<td>2.50 (0.92, 6.77)</td>
<td>0.49 (0.13, 1.77)</td>
<td>1.20 (0.50, 2.87)</td>
</tr>
<tr>
<td>Fortuny, 2006 (16)</td>
<td>0.90 (0.28, 2.85)</td>
<td>0.90 (0.28, 2.85)</td>
<td>0.50 (0.17, 1.41)</td>
<td>0.67 (0.31, 1.41)</td>
</tr>
<tr>
<td>Cerhan, 2005 (40)</td>
<td>1.20 (0.62, 2.31)</td>
<td>0.49 (0.13, 1.77)</td>
<td>0.50 (0.17, 1.41)</td>
<td>0.67 (0.31, 1.41)</td>
</tr>
<tr>
<td>Holly, 2008 (41)</td>
<td>1.20 (0.62, 2.31)</td>
<td>0.49 (0.13, 1.77)</td>
<td>0.50 (0.17, 1.41)</td>
<td>0.67 (0.31, 1.41)</td>
</tr>
<tr>
<td>Zahn, 1995 (46)</td>
<td>1.20 (0.62, 2.31)</td>
<td>0.49 (0.13, 1.77)</td>
<td>0.50 (0.17, 1.41)</td>
<td>0.67 (0.31, 1.41)</td>
</tr>
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</table>

**Notes:**
- REAL, Revised European-American Lymphoma.
- Diabetes without treatment.
- Diabetes treated with insulin.
- Diabetes treated with oral antidiabetic agents.

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Fortuny et al. (16) reported that risk of non-Hodgkin lymphoma among persons with diabetes differed by the diabetic treatment received. Although increased risk was observed among patients who had no treatment and who used oral antidiabetic agents, no elevated risk was suggested for those who used insulin. Studies have suggested that several antidiabetic medications may be linked to increased or reduced risk of cancer (58, 59). However, the literature has been inconclusive, and the association with lymphoma has not been specifically examined. Duration of diabetes may also affect the risk of non-Hodgkin lymphoma. Cerhan et al. (14) reported that risk increased as diabetes duration increased. However, Scotti et al. (44) failed to observe the same. Another potential source of heterogeneity among the study results may be the distribution of non-Hodgkin lymphoma subtypes. Different subtypes may have different etiologic factors (60–62). Table 4 summarized the findings from the literature on the effect of diabetes mellitus on non-Hodgkin lymphoma subtype. Currently available data are limited, and more studies are needed to investigate the association between type 2 diabetes mellitus and different non-Hodgkin lymphoma subtypes.

There is a well-recognized biologic plausibility for an association between type 2 diabetes mellitus and non-Hodgkin lymphoma. Both immunosuppression and chronic inflammation have been implicated in non-Hodgkin lymphoma pathogenesis (3, 63, 64). It is well known that diabetic patients are at increased risk for infections, and suppression of cellular immunity in type 2 diabetes mellitus has long been reported (65, 66). Brody and Merlie (67) reported in 1970 that diabetic lymphocytes showed similar abnormalities in metabolism and DNA synthesis as lymphocytes in chronic lymphocytic leukemia. Numerous epidemiologic studies have linked systemic inflammation to insulin resistance (68–72). Although chronic inflammation may predispose to insulin insensitivity and type 2 diabetes mellitus, emerging data also suggest a regulating role of insulin on the inflammatory response. Insulin regulates the expression of several hepatic proteins that are involved in inflammatory response (6, 7). In a rat model with induced inflammation, insulin treatment suppressed the level of proinflammatory cytokines, such as interleukin-6 and TNF-α (11). The role of inflammation-mediating cytokines in lymphomagenesis is well accepted and is further confirmed by a recent large genetic association study (73). In patients with diabetes or hyperglycemia, treatment with insulin led to a substantial decrease in the levels of inflammatory mediators (9, 10). The state of hyperglycemia is also known to initiate a reactive oxygen species chain reaction and to activate several proinflammatory cytokines, such as interleukin-6 and TNF-α (74–76). Rapp et al. (77) examined the relations between fasting blood glucose and the incidence of several cancers. They found that elevated fasting blood glucose was positively associated with risk of non-Hodgkin lymphoma in men, whereas no association was found in women. We have not identified any studies that have evaluated the relation between direct measures of insulin resistance or of waist circumference and risk of non-Hodgkin lymphoma. Few epidemiologic studies have examined the role of physical activity in non-Hodgkin lymphoma (40, 54, 78–81). An inverse association was reported by several of these studies (40, 54, 78), corroborating the insulin resistance hypothesis. More studies are needed to elucidate the lymphomagenic mechanism of type 2 diabetes mellitus.

This is the first systematic review to comprehensively and systematically evaluate the epidemiologic studies that have looked at the relation between type 2 diabetes mellitus and non-Hodgkin lymphoma. Although this review suggests that there may be increased risk of non-Hodgkin lymphoma associated with having type 2 diabetes mellitus, the evidence is inconclusive. We have identified the design and analytical shortcomings of the included studies and suggest areas that need to be improved to advance knowledge in this area. Cohort studies with prospective data collection and outcome ascertainment are needed to avoid bias from recall, subject selection, and differential non-Hodgkin lymphoma survival. There should be careful control of confounding by joint risk factors for both conditions, including body fat distribution and socioeconomic status. There also needs to be detailed measurement of the diabetes disease history (including the duration of disease, type 1 or type 2, and medication used) and classification of non-Hodgkin lymphoma subtypes. It would also help to stratify by viral risk factors of non-Hodgkin lymphoma, such as human immunodeficiency virus. Improved laboratory measurements (e.g., insulin, blood glucose, and hemoglobin A1c) will help to provide insight into the mechanisms involved. There also need to be studies done in more regions of the world to give us a clearer picture of the relations worldwide. As the incidence of non-Hodgkin lymphoma continues to climb, elucidating the relation between type 2 diabetes mellitus and non-Hodgkin lymphoma has important scientific and public health significance as it may provide insights for novel mechanisms of lymphomagenesis and means of non-Hodgkin lymphoma prevention.

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REFERENCES


