2011-12-29

Diabetes and Risk of Non-Hodgkin's Lymphoma

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A meta-analysis of observational studies

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OBJECTIVE — To examine the epidemiologic association between diabetes and risk of non-Hodgkin's lymphoma (NHL).

RESEARCH DESIGN AND METHODS — We searched MEDLINE for observational studies on the association between diabetes and NHL in adults using the keywords "diabetes" and "lymphoma." Prospective cohort studies that reported relative risks or standardized incidence ratios and case-control studies that reported odds ratios with 95% CIs were included. A random-effects model was used to combine results from the individual studies.

RESULTS — A total of 15 manuscripts (reporting data from 5 prospective cohort and 11 case-control studies) met the inclusion criteria. Combining data from all studies, the risk ratio (RR) of developing NHL in patients with diabetes was 1.19 (95% CI 1.04–1.35). Based on prospective studies, patients with diabetes had an RR of developing NHL of 1.41 (1.07–1.88), without heterogeneity among studies ($I^2 = 34.3\%$; $P > 0.10$). Based on case-control studies, patients with diabetes had an RR of 1.12 (95% CI 0.95–1.31) of developing NHL compared with people without diabetes, with some heterogeneity among studies ($I^2 = 36.28\%$; $P = 0.09$).

CONCLUSIONS — Diabetes is associated with a moderately increased risk of NHL, which is consistent with other reported associations between diabetes and malignancies. Future studies should focus on elucidating potential pathophysiologic links between diabetes and NHL.

Diabetes Care 31:2391–2397, 2008

The incidence of non-Hodgkin's lymphoma (NHL), a heterogeneous group of conditions characterized by uncontrolled growth of monoclonal malignant lymphocytes, has been increasing in Western countries over the last few decades (1). The increase has been more pronounced in whites, men, and the elderly (1). NHL is now the fifth most commonly diagnosed cancer among both men and women and accounts for 4% of all cancer diagnoses (1). Several hypotheses have been proposed to explain this increased incidence, including aging of the population, exposure to pesticides, prolonged survival of patients with immunodeficiency states (including HIV), and increased prevalence of autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Sjögren's Syndrome, and multiple sclerosis).

In parallel with the increasing incidence of NHL, the prevalence of diabetes has increased over the last few decades (2). Diabetes has been associated with increased risk of several malignancies, including endometrial, ovarian, breast, gallbladder, liver, colonic, and pancreatic cancer (3–7), but its relationship with NHL is unclear. Individuals with diabetes are believed to have altered immune function and to be in a relatively immunodeficient state (8), which may contribute to the pathogenesis of lymphoproliferative disorders, such as NHL (9). Furthermore, there is a growing body of evidence linking insulin and IGF-I to cell proliferation, lack of apoptosis in cells, and cell metastasis (10)—phenomena involved in the development and progression of malignancies.

An association between diabetes and NHL was initially reported 40 years ago (11). Since then, several studies have examined this association in different population- and hospital-based settings with inconsistent results. The objective of this study was to perform a systematic review and meta-analysis of observational studies to estimate the risk of NHL in patients with diabetes.

RESEARCH DESIGN AND METHODS

Data search

We conducted a search of MEDLINE (1 January 1980 through 30 April 2008) for observational cohort and case-control studies reporting an association between diabetes and NHL using the keywords "diabetes" and "lymphoma." We searched for additional studies in personal reference lists and citation sections of recovered articles.

Study selection

Two authors (J.M. and J.C.) screened abstracts according to the inclusion criteria. An abstract was judged relevant if it reported original data, was published in the English language, and was from epidemiological studies where the outcome variable was NHL and the predictor variable was diabetes (any type). Prospective cohort studies reporting relative risks or standardized incidence ratios with 95% CIs and case-control studies reporting odds ratios (ORs) with 95% CIs were included in the meta-analysis. Manuscripts reporting only data on Hodgkin's disease and multiple myeloma were excluded because the pathophysiology of these conditions is different from that of NHL (12). If a manuscript included data on other

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Received 7 June 2008 and accepted 20 August 2008.
DOI: 10.2337/dc08-1034

cancers besides NHL, we extracted the data on NHL only. Full-text articles, including letters to the editor, were retrieved and reviewed if a decision on inclusion could not be made based solely on the abstract. Any discrepancies were resolved by consensus in-group conference referencing the original article. When there were multiple publications from the same population, we included data from the most recent one. We did not contact the authors of the original manuscripts for additional data.

Data extraction

The following data were extracted from each study: author, country of origin, publication year, participant characteristics (age and sex), sample size, inclusion and exclusion criteria, and methods of diagnosis of diabetes and NHL. For cohort studies, we extracted the source of cohort, the follow-up period, the source of the expected incidence of NHL, relative risk or standardized incidence ratio with 95% CI, and variables adjusted for in the statistical analysis. For case-control studies, we extracted the source of case and control subjects (e.g., hospital based and population based), OR with 95% CI, and variables adjusted for in the statistical analysis. Ascertainment of exposure (self-reported versus registry based) and extent of multivariate adjustment were used to evaluate study quality. Data were extracted by one author (J.M.) and independently verified by another (A.G.P.).

Data synthesis and analysis

The primary measure was risk ratio (RR) of NHL, calculated using the random effects model (DerSimonian-Laird method), which accounts for heterogeneity among studies (13). Because the absolute risk of NHL is low, the OR in case-control studies mathematically approximates the RR (14); therefore, we report all results as RRs. To assess heterogeneity among the studies, we used the Cochran Q and I^2 statistics; for the Q statistic, a P value <0.10 was considered statistically significant for heterogeneity (15); for I^2, a value $>50\%$ is considered a measure of severe heterogeneity (16). Subgroup analyses were performed for sex and for type of diabetes. We assessed publication bias using the funnel plot, which plots relative risk (or OR) by sample size. When data were not uniformly reported to allow formal statistical analyses, we present the data in a narrative format. Data were analyzed using MIX version 1.7 (17), a comprehensive free software for meta-analysis of causal research data that has been validated against STATA (StataCorp; College Station, TX) and Comprehensive Meta-analysis (Biostat; Englewood, NJ), two of the most utilized meta-analysis software tools.

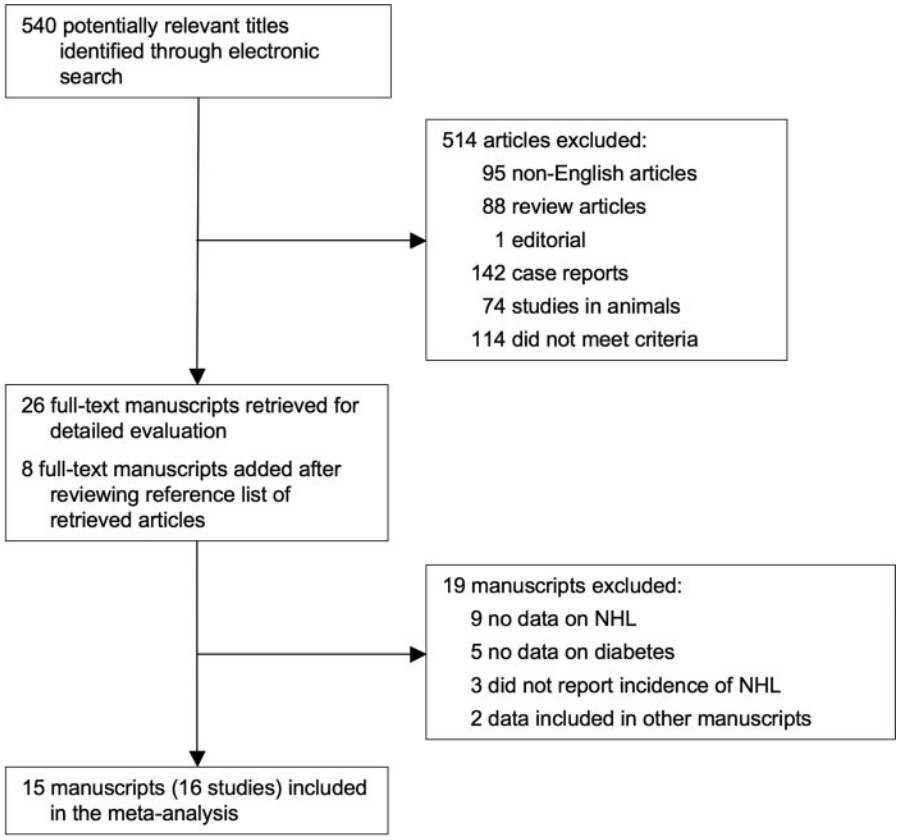

Figure 1—*Search results.*

RESULTS

Search results

A total of 540 abstracts were identified during the initial search (Fig. 1). After review of the abstracts, 514 were ineligible because they were reviews, editorials, case reports, comments, or preclinical studies. After reviewing the reference list of the remaining 26 studies, 8 more studies were considered. After detailed evaluation of the 34 potential manuscripts, 19 manuscripts were excluded for reasons shown in Fig. 1.

Characteristics of prospective studies

We identified five prospective cohort studies of diabetes and risk of NHL (Table 1) (5,6,18–20). Studies were published between 1997 and 2006 and included more than 160,000 participants with diabetes; participants were followed for 6 to 25 years, reporting a total of 337 incident cases of NHL. The diagnosis of diabetes was self-reported in two studies (6,18) and was registry based in three studies (5,19,20). All studies included histologically confirmed cases of NHL. Two studies excluded NHL cases that were reported during the first 1 or 2 years of follow-up to minimize the impact of selection bias (6,20). None of the studies mentioned whether participants with HIV infection were excluded.

Three studies reported relative risk (6,18), whereas the remaining three reported standardized incidence ratio (5,19,20). With the exception of two studies (6,18), investigators did not adjust risk for potential confounders other than age and sex. One study was performed in a women-only cohort (18).

Characteristics of case-control studies

We identified 10 manuscripts reporting data from 11 case-control studies published between 1988 and 2007 (Table 2) (7,21–29). A total of 382 cases of NHL were reported among 4,844 patients with diabetes, whereas a total of 7,974 cases of

NHL were reported among 86,660 control subjects without diabetes. The diagnosis of diabetes was self-reported in all studies. The diagnosis of NHL was pathologically confirmed in all studies with the exception of one study that confirmed the diagnosis of NHL through a review of medical records (27). Control subjects originated from a population-based (7,21,22,26–29) or hospital-based setting (23–25). All studies adjusted their result for age. Eight studies adjusted for sex (21,23–29), two for BMI (7,24), three for ethnicity (7,21,28), two for level of education (7,25), and one for country of origin (29). Four studies excluded individuals with HIV infection (21,24,27,29). Two studies included only men (7,22).

Analyses

After combining data from all studies (prospective and case-control), the RR of NHL in patients with diabetes was 1.19 (95% CI 1.04–1.35) (Fig. 2). Visual examination of the funnel plot revealed minimal asymmetry. In prospective studies, the RR for NHL among patients with diabetes was 1.41 (95% CI 1.07–1.88), without heterogeneity among studies (I^2 = 34.3%; $P > 0.10$). Among case-control studies, the increased risk of NHL among patients with diabetes was not statistically significant (1.12 [0.95–1.31]) but had a mild degree of heterogeneity (I^2 = 36.28%, $P = 0.09$).

Diabetes and NHL by sex

We then combined data from the three prospective (6,18,20) and four case-control (7,22,25,28) studies that reported risk of NHL according to sex. Female patients with diabetes had a statistically significant increased risk of developing NHL (RR 1.38 [95% CI 1.06–1.80]). In men with diabetes, there was no increased risk of NHL (0.98 [0.79–1.22]). No heterogeneity was detected in these subgroup analyses.

Type of diabetes and NHL

Along with one study that identified type of diabetes by national registry (5), several studies used the age of onset of diabetes (18–21,24,29) as a proxy for a presumptive diagnosis of type 1 or type 2 diabetes (Tables 1 and 2). Combining databases from patients with type 1 diabetes (age of onset younger than 30 years), the pooled RR was 1.27 (95% CI 0.82–1.99), without evidence of heterogeneity (I^2 = 0.0%; $P > 0.10$). In patients with type 2 diabetes (age of onset older than 30

Table 1—*Prospective cohort studies of diabetes and risk of NHL*

Authors, year (country)	Cohort	Sex	Age (years)	Type of diabetes	NHL assessment	Mean follow-up (starting to ending year)	*n* with diabetes/ person-years/ *n* NHL cases	Study quality: Definition of diabetes	Study quality: Adjustments
Cerhan et al., 1997 (U.S.)	Iowa Women's Health Study	F	55–69	Type 1 (onset ≤30 years)	National cancer registry	7 (1986–1992)	NR/603/1	Self-reported	Age adjusted
		F	55–69	Type 2 (onset >30 years)	National cancer registry	7 (1986–1992)	NR/13,581/13	Self-reported	Age adjusted
Hjalgrim et al., 1997 (Denmark)	Funen County, Denmark	M/F	NR	Insulin-treated type 2 (onset ≥30 years)	National cancer registry	19 (1973–1992)	772/7,802/6	Prescriptions based	No adjustments
Weiderpass et al., 1997 (Sweden)	Swedish National Inpatient Register	M/F	NR	NR	National cancer registry	24 (1965–1989)	134,098/901,147/237	Hospital discharge diagnosis	No adjustments; no difference according to sex
Swerdlow et al., 2005 (U.K.)	Diabetes UK cohort	M/F	NR	Insulin-treated type 1 (onset <30 years)	National cancer registry	18 (1972–2003)	23,834/NR/14	Registry based	No adjustments
		M/F	NR	Insulin-treated type 2 (onset 30–49 years)	National cancer registry	18 (1972–2003)	5,066/NR/12	Registry based	No adjustments
Khan et al., 2006 (Japan)	Japan Nationwide Cohort	M	40–80	NR	Self-reported (confirmed by cancer registry in about half of cohort)	9 (1988–1997)	1,753/NR/28	Self-reported	Adjusted for age, BMI, smoking, and alcohol use
		F	40–80	NR	Self-reported (confirmed by cancer registry in about half of cohort)	9 (1988–1997)	1,541/NR/19	Self-reported	Adjusted for age, BMI, smoking, and alcohol use

NR, not reported.

Table 2—*Case-control studies of prevalence of diabetes among patients with NHL*

Authors, year (country)	Sex	Age (years)	Cases (ascertainment period), *n*	Control subjects, *n*	Exposure, type of diabetes	Study Quality: Exposure, ascertainment method	Study Quality: Adjustments
Bernstein et al., 1988 (U.K.)	M/F	19–75	Incident NHL (1979–1982), 619	Population based, 619	Type NR	Self-reported	Age, sex, race, residence
Cartwright et al., 1988 (U.K.)	M/F	NR	NHL (1979–1984), 458	Hospital based, 742	Type NR	Self-reported	Age, sex, residence
Zham et al., 1995 (U.S.) Kansas cohort	M	NR	NHL (1976–1982), 169	Population based, 936	Type NR	Self-reported	Age
Zham et al., 1995 (U.S.) Iowa/Minnesota cohort	M	NR	NHL (1980–1983), 577	Population based, 1,146	Type NR	Self-reported	Age
Vineis et al., 2000 (Italy)	M/F	20–74	NHL (1990–1993), 1,388	Population based, 1,718	Type NR	Self-reported	Age, sex
Cerhan et al., 2005 (U.S.)	M/F	20–74	Incident NHL (1998–2000), 703	Population based, 538	Type 1 (onset ≤ 30 years)	Self-reported	Age, sex, ethnicity, study site. HIV+ excluded
			Incident NHL (1998–2000), 753	Population based, 587	Type 2 (onset > 30 years)	Self-reported	Age, sex, ethnicity, study site. HIV+ excluded
Fortuny et al., 2005 (Spain)	M/F	17–96	Incident NHL (B-cell) (1998–2002), $n = 247$	Hospital based, 595	Type 2 (onset > 30 years)	Self-reported	Age, sex, study center. HIV+, post-transplant excluded
	M/F	17–96	Incident NHL (T-cell) (1998–2002), 45	Hospital based, 595	Type 2 (onset > 30 years)	Self-reported	Age, sex, study center. HIV+, post-transplant excluded
Rousseau et al., 2005 (Canada)	M	35–70	Incident NHL (1979–1985), 195	Population based, 509	Type NR	Self-reported	Age, BMI, ethnicity, income, education, farming
Smedby et al., 2006 (Denmark and Sweden)	M/F	18–74	NHL (2000–2002) and (1999–2002), 3,007	Population based, 340	Type 1 (onset < 30)	Self-reported	Age, sex, country. HIV+, post transplant, hematopoietic malignancies excluded
Lin et al., 2007 (Taiwan)	M/F	>30	Incident NHL (2000–2004), 242	Population based, 71,379	Type NR	Self-reported	Age, sex, smoking, alcohol, hypertension. HIV + excluded
Scotti et al., 2007 (Italy)	M/F	17–85	NHL (2000–2004), 671	Hospital based, 1,799	Type NR	Self-reported	Age, sex, study site, residence, education

NR, not reported.

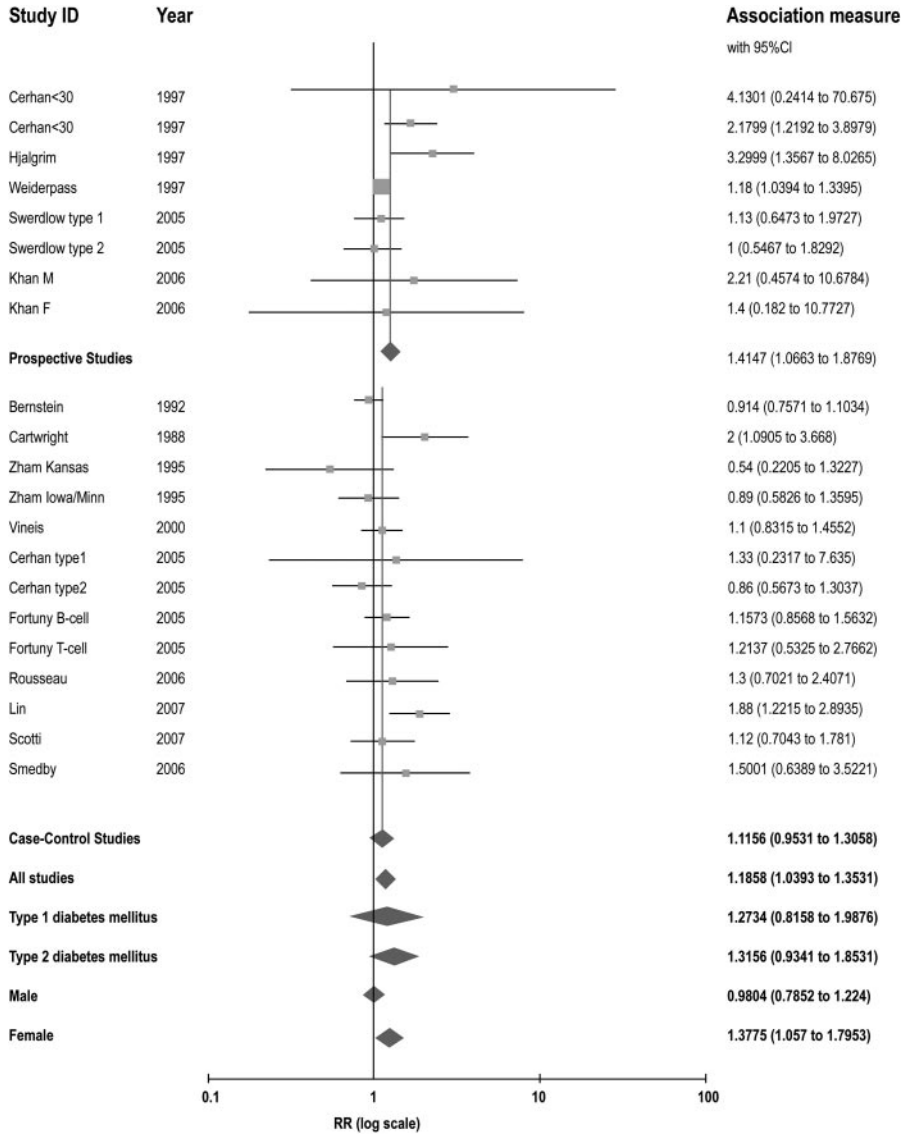

Figure 2—*Risk estimates of developing NHL for patients with diabetes compared with control subjects (patients without diabetes).*

years), the pooled RR was 1.32 (0.93–1.85), but with heterogeneity between studies ($I^2 = 57.9\%$; $P = 0.04$).

Duration and severity of diabetes and NHL

There were limited and conflicting data on duration and severity of diabetes and risk of NHL, which were not uniformly reported, making formal statistical analyses impossible. Two studies reported a positive association between diabetes and risk of NHL with increasing duration of diabetes (5,18); however, in another study, the risk of NHL continuously decreased with increasing time of follow-up (20). In case-control studies, Fortuny et al. (24) showed an increased OR of NHL in individuals who had diabetes for more than 12 years compared with patients without diabetes, whereas Scotti et al. (25) reported no increased risk of NHL with longer duration of diabetes.

Diabetes therapy and NHL

There were limited data on therapy for diabetes and risk of NHL, which did not allow for formal statistical analyses. Cerhan et al. (18) reported an increased risk of NHL in women with diabetes who were on oral antidiabetic therapy (relative risk 3.43 [95% CI 1.67–7.07]), but the risk became nonstatistically significant in women who were on oral antidiabetic therapy and concurrent insulin (relative risk 2.13 [0.78–5.79]). Fortuny et al. (24) reported an increased risk in patients with diabetes not on pharmacological therapy (OR 1.73 [1.11–2.68]), whereas the risk in patients treated with oral antidiabetic therapy and/or insulin was not statistically significant.

CONCLUSIONS— Our analyses showed that patients with diabetes have an increased risk of developing NHL compared with those without diabetes. Although the size of the increased risk was moderate, based on the projected increase in the incidence and prevalence of diabetes (2), our findings suggest a concurrent increase in the incidence of NHL.

NHL is a malignant disorder characterized by an uncontrolled growth of monoclonal lymphocytes, observed most commonly within the lymph nodes. NHL is a heterogeneous condition and comprises several different morphologic subtypes with distinct clinical behaviors and outcomes. The increase in NHL incidence over the last few decades is part of a longer trend documented since 1950 (1), and improved medical technology and changing systems of diagnostic classification can explain only part of it. Many medical conditions have been associated with increased risk of developing lymphoma, including congenital or acquired immunodeficiency states (HIV [30] and post transplant [31]), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, and Sjögren's Syndrome) (32,33), and different infectious agents (34) such as human T-cell lymphotrophic virus type I, hepatitis C virus, *Helicobacter pylori*, *Chlamydia psitacii*, and *Borrelia sp*. What most of these conditions have in common is immune dysregulation (9). Indeed, the risk of developing NHL among patients in immunosuppressed states is several times greater than that of the general population (30,31). However, these immunocompromized states are relatively rare and cannot fully explain the long-term and large increase in NHL incidence. Our findings of an increased risk of NHL associated with diabetes may provide an explanation for the increased incidence of NHL not associated with rare immunosuppressed states. It is increasingly recognized that not only type 1 but also type 2 diabetes is characterized by immune dysfunction related to impaired neutrophil activity and changes in cellular and humoral immunity (35), which may, at least in part, account for the increased risk of NHL that we found in this study.

The majority of patients with type 2 diabetes are obese; therefore, the observed association between diabetes and NHL may be mediated by metabolic derangements associated with the obese state. It is increasingly recognized that excess body fat is associated with increased risk of common and less common malignancies (36). A recent meta-analysis also found an increased risk of NHL with excess body weight (37). The increase in NHL associated with excess body weight might be mediated by changes in circulating adipocytokines, such as adiponectin and leptin. These cytokines are thought to be involved in immunity and inflammation and can alter the balance between cell proliferation and death. Studies in vitro and in animal models indicate that adiponectin has anti-inflammatory properties and reduces cell proliferation, whereas leptin has proinflammatory properties and promotes the growth of certain cancer cells. In vitro studies have shown that leptin stimulates the proliferation of normal hematopoietic cells as well as circulating monocytes producing proinflammatory cytokines, such as tumor-necrosis factor and interleukin.

Treatment of diabetes, rather than the disease pathophysiology itself, may also be of etiologic importance. For example, adverse reactions to sulfonylureas include agranulocytosis, aplastic anemia, bone marrow aplasia, and hemolytic anemia, but these clinically apparent conditions are relatively rare, and tumor-inducing effects have not been reported. Furthermore, various types of insulin are also known to be immunogenic. Based on the reviewed studies, we were unable to reach any conclusions on a potential link between therapy and NHL risk. Also, any potential treatment effects may be confounded by duration of the disease.

The increased risk of NHL in patients with diabetes was observed in both prospective and case-control studies but was statistically significant only among prospective studies. The disparity may be attributed to a variety of study-specific factors, including the relatively small number of cases, the failure to take confounding factors into account, and recall bias that may have resulted in misclassifications of type and duration of diabetes.

Our subgroup analysis showed that the risk of NHL in women with diabetes is 38% higher compared with women without diabetes, but the risk in men was not increased. These findings are in contrast with the reported increased ratio of lymphoproliferative disorders in men compared with women. Although our findings may represent a true association between diabetes and NHL that occurs only in women, our results may be limited by the small number of studies that reported data by sex.

Based on the age of diagnosis as a proxy for type of diabetes, the risk of NHL appeared to be higher in patients with type 2 diabetes (older than 30 years) than in those with type 1 diabetes (younger than 30 years). However, the results for neither subgroup analysis were statistically significant.

Our study has certain limitations based on the quality of the published studies. First, although some studies confirmed the diagnosis of diabetes, most used self-report of diabetes as the predictor. A positive self-report for diabetes is generally quite accurate in epidemiologic studies (38). Second, the type of diabetes was not confirmed. Most studies used age as a proxy criterion for the two most common types of diabetes (type 1 and type 2). Severity, duration, and treatment of diabetes were also not reported in most studies. Third, our observed association may be due to confounding, as most prospective studies did not control for potential confounders, including HIV status of participants. Finally, our systematic review was restricted to articles in the English language, which may have influenced the results. However, there is also evidence that some countries publish unusually high proportions of positive results (39), which would introduce publication bias.

In conclusion, our analysis shows that diabetes is associated with moderately increased risk of NHL, which is consistent with other reported associations between diabetes and malignancies. Although the relative risk is moderate, given the rapidly increasing incidence and prevalence of diabetes, the number of incident cases of NHL attributed to diabetes can potentially be very high. Future studies should focus on elucidating potential pathophysiologic links between diabetes and NHL.

Acknowledgments— A.G.P. is supported by National Institutes of Health grants R01-DK76092, R0179003, and R2178867.

Portions of the manuscript were presented at the 68th Scientific Sessions of the American Diabetes Association, San Francisco, California, 6–10 June 2008.

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