Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

Metformin Is Not Associated with Incidence Risk of Non-Hodgkin Lymphomas among Diabetic Patients

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Abstract

Background: Several epidemiological studies have shown a positive association between diabetes and increased risk of non-Hodgkin lymphoma (NHL), but the effect of diabetic treatment drugs such as metformin on the risk is unknown.

Methods: We conducted a population-based nested case–control study involving 878 NHL cases and 4,364 controls diagnosed with diabetes. Use of metformin and other medications before diagnosis and medical condition histories were assessed using administrative databases. We used conditional logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for use of metformin, adjusting for confounders.

Results: Risk of total NHLs is not associated with ever use of metformin (OR, 0.93; 95% CI, 0.79–1.10) among diabetic patients. NHL subtypes were also not associated with metformin use.

Conclusions: Metformin use is not associated with overall or subtype NHL risk among diabetic patients.

Impact: NHLs are etiologically heterogeneous and larger scale studies are warranted to test the potential effect of metformin by NHL subtype. *Cancer Epidemiol Biomarkers Prev; 27(5); 610–2.* *©2018 AACR.*

Introduction

Epidemiological studies have consistently shown associations between diabetes mellitus (DM) and an increased risk of some cancers (e.g., liver, pancreas, endometrium, colon and rectum, breast, bladder; ref. 1). Potential preventative effects of antidiabetic drugs, such as metformin, on cancer have thus been hypothesized. Epidemiological evidence exists on the association between metformin and decreased incidence risk of overall and specific cancers (e.g., pancreatic and hepatocellular cancers) among diabetic patients (2).

Immunosuppression, chronic inflammation, and lymphocyte dysfunction occurring in DM patients have been associated with the development of lymphoma, indicating a plausible link between DM and non-Hodgkin lymphoma (NHL; ref. 3). Several epidemiological studies have found that DM was associated with increased NHL incidence risk (3, 4). We have not found studies on the association between metformin and NHL. We aimed to study the association between metformin use and NHL risk in Manitoba, Canada.

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Materials and Methods

Data sources

We conducted a population-based nested case–control study using cancer registry and health service administrative databases in Manitoba, Canada. The methods have been described in detail previously. Cases and controls were included if they were 40 years or older and had been diagnosed with diabetes (based on ICD-8/9 code 250.x and ICD-10 code E11-E14). Participants must have been registered with Manitoba Health for no less than five years before the index date to be included in the study, to ensure that the histories of exposure, if any, are of adequate length. NHL cases were identified from the Manitoba Cancer Registry. For each case, five controls are matched on gender, age, region of residence, date of diabetes diagnosis, and length of registration with the provincial health insurance, using the risk set sampling approach. Case and control records were linked to prescription drug, hospital discharge, and physician claim databases. Medication use histories were ascertained for the period between the index date and April 1, 1995, or the coverage initiation date, whichever was later. Metformin use during the 1-year period before the index date was excluded to minimize protopathic bias—a drug can be used to target early disease symptoms.

We used conditional logistic regression models to calculate odds ratios (ORs) and 95% confidence intervals (CIs). The sample size ensured a greater than 80% statistical power to detect an OR between 0.6 and 1.5. We assessed potential confounders using the change-in-estimation method and clinical relevance. We adjusted for chronic cardiovascular diseases, use of statin and non-statin lipid-lowering drugs, aspirin, non-aspirin antisteroidal anti-inflammatory drugs (NSAIDs), income, and number of physician visits 5 years before diagnosis in the final analysis models. Separate analyses were undertaken for Total NHL and the

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main NHL subtypes including chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL), diffuse large B-cell lymphoma (DLBCL), plasma cell neoplasms (PCN), follicular lymphoma (FL), and other NHLs. All data analysis was performed in Stata 14 (StataCorp LLC).

Results

In total 878 diabetic NHL cases were included. Cases and controls were similar in terms of demographics, medical condition and medication use histories, but cases tended to have more physician visits during the past 5 years before the index date (Table 1). About half of diabetes patients (cases and controls) were prescribed metformin. Approximately 16% and 49% of patients used insulin and other oral hypoglycemic drugs, respectively. As shown in Table 2, metformin use was not associated with incidence risk of Total NHL (OR, 0.93; 95% CI, 0.79–1.10). There were also no associations between metformin use and incidence risk of NHL subtypes.

Discussion

We did not find an association between metformin use and NHL incidence risk among diabetic patients. A recent study reported an inverse association between metformin use and NHL risk among females, with an OR of 0.76 (95% CI, 0.64–0.91; ref. 5). Unlike the present study, which is conducted among diabetic patients only, the recent study included all types of patients. Caution in interpreting the finding from the recent study is also warranted due to the lack of clarity for epidemiological methodology and the simultaneous testing of multiple hypotheses in the study.

Epidemiological studies demonstrated that diabetic patients treated with metformin had lower incidence or mortality risk for several cancers, including colorectal, pancreatic, and hepatocellular cancers (6). Metformin has been associated with a reduced risk of progression from monoclonal gammopathy of undetermined significance to multiple myeloma (7). Metformin's anticancer mechanisms are unclear, but may involve multiple pathways, including suppressing tumor cell growth via AMPK activation and inhibiting proliferation via the mTOR pathway. Those effects were demonstrated in lymphoma cells (8), indicating the biological possibility for metformin's effect in preventing lymphoma and in improving lymphoma progression. Despite the experimental study evidence, our epidemiological study findings do not support the association in NHLs.

Table 1. Socioeconomic and clinical characteristics of diabetic NHL cases and diabetic cancer-free controls

Characteristics	Case ($N = 878$)	Control ($N = 4,364$)
Male	492 (56.0%)	2,447 (56.1%)
Age group (y)		
40–54	58 (6.6%)	282 (6.5%)
55–64	175 (19.9%)	872 (20.0%)
65–74	272 (31.0%)	1,380 (31.6%)
75+	373 (42.5%)	1,830 (41.9%)
Income quintile		
Q1 (lowest)	183 (20.8%)	1,012 (23.2%)
Q2	214 (24.4%)	905 (20.7%)
Q3	172 (19.6%)	890 (20.4%)
Q4	136 (15.5%)	709 (16.2%)
Q5 (highest)	122 (13.9%)	600 (13.7%)
Unknown	51 (5.8%)	248 (5.7%)
Ever use of medications		
Metformin	455 (51.8%)	2,262 (51.8%)
Insulins	136 (15.5%)	700 (16.0%)
Other oral hypoglycemic drugs	428 (48.7%)	2,116 (48.5%)
Statin	597 (68.0%)	3,020 (69.2%)
Non-statin lipid-lowering drugs	127 (14.5%)	614 (14.1%)
Aspirin	336 (38.3%)	1,657 (38.0%)
Non-aspirin NSAIDs	652 (74.3%)	3,162 (72.5%)
Any NSAIDs	712 (81.1%)	3,505 (80.3%)
Medical conditions		
Chronic cardiovascular disease (excluding hypertension)	69 (7.9%)	279 (6.4%)
Hypertension	72 (8.2%)	366 (8.4%)
Number of physician visits 5 years before index date		
1–34	119 (13.6%)	1,056 (24.2%)
35–54	227 (25.9%)	1,100 (25.2%)
55–84	264 (30.1%)	1,131 (25.9%)
85+	268 (30.5%)	1,077 (24.7%)

Table 2. Adjusted odds ratio (95% CI) of the association between metformin use and NHL incidence risk by subtype

NHL diagnosis	Number of cases	Adjusted OR (95% CI)
Total NHL	878	0.93 (0.79–1.10)
CLL/SLL	213	0.85 (0.61–1.18)
DLBCL	177	0.79 (0.55–1.15)
Plasma cell neoplasms	166	0.92 (0.63–1.35)
Follicular lymphoma	111	1.30 (0.82–2.06)
Other NHLs	211	1.01 (0.72–1.42)

NOTE: Adjusted for sex, age, region of residence, length of registration with the provincial health insurance, length of diagnosed diabetes, income quintile, number of physician visits 5 years before the index date, insulin use, other oral hypoglycemic drug use, statin use, non-statin lipid-lowering drug use, non-aspirin non-steroidal anti-inflammatory drug use and aspirin and derivatives use.

Disclosure of Potential Conflicts of Interest

V. Banerji reports receiving commercial research grants from Lundbeck, Gilead, and Janssen and is a consultant/advisory board member for Gilead, Abbvie, and Janssen. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred. The content is solely the responsibility of the authors and does not necessarily represent the official views of Research Manitoba.

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