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Original Research

Time-Varying Risk for Breast Cancer Following Initiation of Glucose-Lowering Therapy in Women with Type 2 Diabetes: Exploring Detection Bias

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ABSTRACT

Objectives: To explore detection bias in the association between glucose-lowering therapies and breast cancer in a cohort of women with type 2 diabetes.
Methods: This was a retrospective, population-based cohort study. We identified new users of metformin, sulfonylureas, thiazolidinediones and insulin during the index period of January 1, 2003, to December 31, 2010. The main outcome was incident breast cancer, and patients were followed up from drug exposure index date until death, diagnosis of another type of cancer, termination of medical insurance or December 31, 2010. To explore detection bias, we split follow-up time into 2 discrete time periods of 0 to 3 months and 3 months to 6 years after drug index date. We performed time-varying Cox regression analyses, including duration of cumulative drug exposure and ever/never drug exposure for each glucose-lowering therapy into our model. The reference was no use of the same drug-exposure category.
Results: There were 22,169 women with type 2 diabetes, with a mean (SD) age of 53.0 (9.2) years and mean (SD) follow up of 2.2 (1.5) years. Hazard ratios for breast cancer in the first 3 months following initiation of metformin, sulfonylurea or thiazolidinedione were 0.66 (0.43 to 1.02), 0.74 (0.44 to 1.25) and 0.67 (0.38 to 1.18), respectively. In the later period of 3 months to 6 years following drug start, hazard ratios (95% CI) for breast cancer were 1.00 (0.98 to 1.02), 1.01 (0.98 to 1.03) and 0.98 (0.95 to 1.01) for metformin, sulfonylurea and thiazolidinedione cumulative exposure, respectively.
Conclusions: Our findings suggest that no detection bias exists for glucose-lowering therapies and breast cancer in this population.

Mots clés :
cancer du sein
étude de cohorte
épidémiologie
traitements hypoglycémiants
diabète de type 2

RÉSUMÉ

Objectifs : Examiner le biais de détection de l'association entre les traitements hypoglycémiants et le cancer du sein dans une cohorte de femmes atteintes du diabète de type 2.
Méthodes : Il s'agissait d'une étude rétrospective de cohorte en population générale. Nous avons relevé les nouvelles utilisatrices de metformine, de sulfonylurée, de thiazolidinédione et d'insuline durant la période de l'indice d'exposition allant du 1er janvier 2003 au 31 décembre 2010. Le critère de jugement principal était l'incidence du cancer du sein. Les patientes étaient suivies à partir de la date de l'indice d'exposition au médicament jusqu'à la mort, au diagnostic d'un autre type de cancer, à la cessation de l'assurance maladie ou au 31 décembre 2010. Pour examiner le biais de détection, nous avons divisé le temps de suivi en 2 périodes distinctes de temps, à savoir de 0 à 3 mois et de 3 mois à 6 ans après la date de l'indice d'exposition au médicament. Nous avons réalisé les analyses de régression de Cox comportant des covariables à variation temporelle, dont la durée cumulative de l'exposition au médicament et la durée d'exposition/de non-exposition au médicament de chacun des traitements hypoglycémiants dans notre modèle. La référence était la non-utilisation de la même catégorie d'exposition au médicament.
Résultats : Il y avait 22 169 femmes atteintes du diabète de type 2, dont l'âge moyen (ÉT) était de 53,0 (9,2) ans et dont le suivi moyen (ÉT) était de 2,2 (1,5) ans. Les rapports de risque de cancer du sein au cours des 3 premiers mois qui ont suivi l'introduction de la metformine, de la sulfonylurée ou de la thiazolidinédione étaient respectivement de 0,66 (0,43 à 1,02), de 0,74 (0,44 à 1,25) et de 0,67 (0,38 à

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1,18). Dans la période ultérieure de 3 mois à 6 ans après le début du médicament, les rapports de risque (IC à 95 %) de cancer du sein étaient respectivement de 1,00 (0,98 à 1,02), de 1,01 (0,98 à 1,03) et de 0,98 (0,95 à 1,01) pour l'exposition cumulative à la metformine, à la sulfonylurée et à la thiazolidinédione. *Conclusions :* Nos conclusions suggèrent qu'aucun biais de détection n'existe en ce qui concerne les traitements hypoglycémiants et le cancer du sein chez cette population.

Introduction

Women with type 2 diabetes have a moderately elevated risk for breast cancer; however, this effect appears to be confined to postmenopausal women (1). The potential moderating effect of various glucose-lowering therapies on breast cancer risk in women with type 2 diabetes is poorly understood. There has been particular interest in the effects of metformin on breast cancer outcomes, and a recent meta-analysis of observational studies suggests a possible protective role of metformin on breast cancer risk in postmenopausal women with type 2 diabetes (2). Two other recently conducted meta-analyses reported a significantly decreased risk for breast cancer associated with thiazolidinedione use (3) and a neutral effect with ever-exposure to any type of insulin (4).

An important factor to consider when exploring the association between drug exposure and breast cancer risk in women with type 2 diabetes is whether a possible detection bias might exist following initiation of glucose-lowering therapies (5). Previous research by our group demonstrated detection bias for most cancers following diagnoses of type 2 diabetes (6–8). Although people with type 2 diabetes are at increased risk for many cancers, this risk is particularly elevated at the time of diabetes diagnosis and subsequently levels off over time (6–8); thus, detection bias following onset of type 2 diabetes may contribute to an overestimation of cancer risk and should, therefore, be accounted for in observational studies. There is limited literature exploring whether a similar detection bias exists following initiation of glucose-lowering therapies (9,10). One study found that the highest risk for cancer occurred within the first 30 days of initiating treatment for all glucose-lowering therapies, followed by a subsequent decline in risk that was comparable to that of the background population, after only 6 to 12 months of therapy (9). The other study observed a similar pattern of detection bias following initiation of insulin therapy in people with type 2 diabetes (10). Therefore, both these studies highlight the possibility that any previously reported association between glucose-lowering therapies and an increased risk for cancer may have been overestimated; however, both studies were conducted in Denmark and, thus, may reflect specific treatment patterns in that population.

Using a retrospective population-based cohort of women with type 2 diabetes from the United States, our objective was to determine the risk for breast cancer among new users of glucose-lowering therapies, with a particular focus on whether detection bias exists following initiation of glucose-lowering therapies.

Methods

Data source

We used data from a large United States claims and integrated laboratory database that included employed, commercially insured patients from all 50 states (Clinformatics™ Data Mart Database (OptumInsight, Life Sciences Inc), Maryland, United States). Patient-level data are collected directly from the clinical encounters, which provide unique, clinically rich sources of information. The database has been used in numerous epidemiologic studies and includes deidentified longitudinal data about patients, including administrative and demographic data (types of insurance plans, sex, ages, dates of eligibility, incomes); all billable medical service claims, including inpatient and outpatient visits and medical procedures (deidentified physician and facility identifier, date and place of service, cost of service, admission and discharge dates, procedure and diagnosis codes); all laboratory tests and results; and pharmacy claims data (deidentified prescribing physician, drug dispensed based on national drug codes, quantity and date dispensed, drug strength, days' supply, cost of service) (11–15). All clinical diagnoses are recorded according to the International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM) codes and procedure codes (according to ICD-9 and Current Procedural Terminology-4 codes). The database contains more than 13 million annual lives. We deidentified and accessed the data by using protocols compliant with the Health Insurance Portability and Accountability Act. This study was approved by the ethics review board of the University of Alberta, Edmonton, Alberta, Canada, and the New England Institutional Review Board, United States.

Study population and time periods

We initially identified a prevalent cohort of patients with diabetes (N=429,486) during the index period of January 1, 2003, to December 31, 2010. Diabetes index dates were based on the established case definition for the Canadian National Diabetes Surveillance System (NDSS) (16) or any glucose-lowering therapy use, whichever date came earlier. Using the NDSS criteria, diabetes index date was defined as the first of 1) a hospital admission for diabetes (ICD-9 code 250) or 2) the second of 2 physician fee-for-service claims for diabetes (ICD-9 code 250) within a 2-year period (16). We excluded women with services claims for gestational diabetes (ICD-9 648.8). From our prevalent diabetes cohort, we identified patients who had ever used any of the following glucose-lowering therapies: metformin, sulfonylurea (SU), thiazolidinedione (TZD) or insulin (N=268,766) during the index period. From this group, we created inception cohorts of new users for each of metformin, SU, TZD or insulin by applying a 2-year washout for all glucose-lowering therapies prior to each drug exposure index date (n=52,614). Therefore, all patients in the analyses were therapy-naive. We excluded patients who had diagnoses of any type of cancer within 2 years prior to each drug exposure index date (n=51,543). We further excluded all men and any women who were younger than 30 years of age and who had started on insulin as their first antidiabetic agent to arrive at our final cohort of women with type 2 diabetes (n=22,169).

Outcomes

Our main outcome was incident breast cancer (ICD-9 codes 174, 233.0, 238.3 and 239.3). Patients were followed up from their drug exposure index date and censored on death, diagnosis of another type of cancer, termination of medical insurance or December 31, 2010, providing a maximum possible follow up of 6 years. We did not censor switch of therapy because individuals switching therapy are still at risk for breast cancer, and switch of therapy may be related to breast cancer.