Diabetic Pharmacotherapy and Endometrial Cancer Risk Within a Publicly Funded Health Care System

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Abstract

Objective: There is conflicting evidence regarding the association between metformin and endometrial cancer risk. The objective of this study was to evaluate the association between type of diabetic pharmacotherapy and endometrial cancer risk within a population-based study. The hypothesis was that metformin was associated with the lowest risk.

Methods: This was a nested case-control study using data from the BC Cancer Registry (2000–2009) and from a province-wide prescription network (PharmaNet) since 1996. Patients were classified by drug exposure (metformin, thiazolidinediones, secretagogues, with or without insulin). The primary analysis was a conditional logistic regression to estimate the odds ratios for endometrial cancer in the drug exposure groups. Sensitivity analysis was carried out to account for uncertainty regarding various parameters. The secondary analysis evaluated the effect of dosage using a principal components analysis.

Results: The study cohort comprised 492 cases and 4404 controls. The primary analysis revealed no difference in endometrial cancer risk between those using metformin and those prescribed other classes of medications (OR 1.5, 95% CI 0.9 to 2.4). Women receiving all classes of medications had almost a two-fold increase in risk (OR 1.9, 95% CI 1.1 to 3.3). The secondary analysis revealed an increased risk associated with a greater duration of treatment and number of prescriptions (OR 1.3, 95% CI 1.2 to 1.4).

Conclusion: In this population-based study, metformin was not associated with a decreased endometrial cancer risk. Women receiving multiple types of medications over a long time had the highest risk, implying that the extent of insulin resistance, rather than the effect of any specific medication, drives endometrial cancer risk.

Key Words: Endometrial cancer, insulin-sensitizing agents, metformin, secretagogues, population-based

Competing interests: None declared.

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Résumé

Objectifs : Les données sur l'association entre la metformine et le risque de cancer de l'endomètre sont contradictoires. Cette étude en population générale visait à évaluer le lien entre le type de pharmacothérapie du diabète et le risque de cancer de l'endomètre. Notre hypothèse était que la metformine serait associée au risque le plus faible.

Méthodologie : Nous avons réalisé une étude cas-témoin emboîtée à partir de données du BC Cancer Registry (2000-2009) et d'un réseau provincial d'ordonnances, PharmaNet (données depuis 1996). Nous avons classé les patientes par médicaments auxquels elles avaient été exposées (metformine, thiazolidinediones, sécrétagogues, avec ou sans insuline). En analyse primaire, nous avons effectué une régression logistique conditionnelle afin d'estimer le rapport de cotes pour le cancer de l'endomètre dans les différents groupes, puis une analyse de sensibilité en vue de tenir compte des incertitudes entourant divers paramètres. En analyse secondaire, nous avons évalué l'effet de la posologie au moyen d'une analyse en composantes principales.

Résultats : La cohorte comptait 492 cas et 4 404 témoins. L'analyse primaire n'a révélé aucune différence entre le risque de cancer de l'endomètre chez les femmes prenant de la metformine et le risque chez celles prenant des médicaments d'autres catégories (rapport de cotes [RC] : 1,5; intervalle de confiance [IC] à 95 % : 0,9-2,4). Les femmes recevant des médicaments de toutes les catégories voyaient leur risque presque doubler (RC : 1,9; IC à 95 % : 1,1-3,3). L'analyse secondaire a montré une augmentation du risque en fonction de la durée du traitement et du nombre de médicaments (RC : 1,3; IC à 95 % : 1,2-1,4).

Conclusion : Dans cette étude en population générale, la metformine n'était pas associée à un risque plus faible de cancer de l'endomètre. Les femmes prenant plusieurs types de médicaments sur une longue période couraient le risque le plus élevé, ce qui laisse croire que le risque de cancer de l'endomètre n'est pas fonction de l'effet du médicament utilisé, mais bien de l'importance de la résistance à l'insuline.

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INTRODUCTION

Women with diabetes have at least a two-fold increase in risk of endometrial cancer compared with the general population.[1–3] While endometrial cancer risk is modified by a number of variables, including age, BMI, physical activity, history of smoking, and use of oral contraceptives, it is also possible that pharmacotherapy could affect this risk. Metformin is commonly prescribed as initial pharmacotherapy in type 2 diabetics. It is known to have beneficial effects in women with polycystic ovary syndrome and metabolic syndrome.[4] These benefits suggest that prescribing metformin could reduce the risk of endometrial cancer. Metformin may have several mechanisms for reducing cancer risk, including attenuation of estrogen-dependent endometrial proliferation,[5,6] activation of LKB1 in the activated protein kinase pathway, which could inhibit cell proliferation,[7] and activation of the AMPK pathway in hepatocytes and skeletal muscle, which reduces circulating glucose and insulin levels, in turn reducing cancer risk.[8] In contrast, hyperinsulinemia and overexpression of insulin receptor isoforms have been associated with endometrial cell growth[9] and endometrial cancer risk.[10] These findings have not necessarily translated into differences in risk estimates among various types of diabetic pharmacotherapy. Two United States-based studies[11,12] and one United Kingdom-based study[13] found no reduction in endometrial cancer risk associated with use of metformin, but a Taiwanese study reported a significant reduction.[14]

Our objective was to evaluate the association between type of diabetic pharmacotherapy and endometrial cancer risk using a population-based study within a single-payer publicly funded health care system. We hypothesized that metformin monotherapy would be associated with a reduced risk of endometrial cancer compared with other categories of medications (thiazolidinediones or insulin secretagogues, with or without insulin).

ABBREVIATIONS

AMPK	activated protein kinase
ISA	insulin-sensitizing agent
PC	principal component
PCA	principal components analysis
PCOS	polycystic ovary syndrome
TZD	thiazolidinedione
WHI	Women's Health Initiative

METHODS

The study inception cohort was derived from all women in British Columbia who had been prescribed diabetic pharmacotherapy between January 1, 1996 and December 31, 2009. Prescription data were obtained from a province-wide prescription network (PharmaNet), which has recorded every prescription processed in the province since January 1, 1996. We excluded women who had been prescribed insulin as their first medication as we assumed these women had type 1 diabetes. We did not have the date of diabetes diagnosis nor did we have details on women with diabetes who were never prescribed pharmacotherapy. All incident cases of endometrial cancer from January 2000 to December 2009 were ascertained from the BC Cancer Registry. Unlike a hospital registry or administrative database, the BC Cancer Registry includes demographic and diagnostic information on all cases of cancer diagnosed among residents in British Columbia. The province has a population-based cancer control program which provides access to standardized cancer care for the entire population. The PharmaNet and BC Cancer Registry datasets were linked using a probabilistic linkage based on personal health number (a unique health care number assigned to all residents of BC), last name, and date of birth. Cases were restricted to those whose first prescription was at least one year prior to their initial diagnosis of endometrial cancer (date of endometrial biopsy or dilatation and curettage or date of surgery). We excluded those with a previous diagnosis of cancer prior to starting pharmacotherapy in order to reduce the possibility of increased surveillance and detection bias among these women.

We implemented a time-matched nested case-control study by selecting up to 10 controls for each case, chosen randomly from a set matched for year of birth and the year and month of first prescription in the PharmaNet database (cohort entry). Each control was then assigned an index date corresponding to the diagnosis date for the matched case, which resulted in matching for length of follow-up. This enabled us to mitigate immortal time bias by considering exposure to drugs as a time-dependent variable. Immortal time bias was described by Suissa et al. as a bias with time-fixed analyses that inappropriately classify unexposed person-time as exposed.[7,15,16] For those who had no matched controls using the above criteria, controls with the same year of birth ± 1 year and the same year and month of cohort entry were chosen. Alternatively, controls were chosen with the same year of birth but within ± 6 months of cohort entry. This reduced bias due to different times of exposure opportunity (time window bias). A time-matched nested case-control study design was chosen over a time-varying survival analysis because it did not impose the assumption of proportional hazards.