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# Metformin and breast cancer stage at diagnosis: a population-based study

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## ABSTRACT

**Purpose** The objective of the present study was to use a large, population-based cohort to examine the association between metformin and breast cancer stage at diagnosis while accounting for mammography differences.

**Methods** We used data from Ontario administrative health databases to identify women 68 years of age or older with diabetes and invasive breast cancer diagnosed from 1 January 2007 to 31 December 2012. Adjusted logistic regression models were used to compare breast cancer stage at diagnosis (stages I and II vs. III and IV) between the women exposed and not exposed to metformin. We also examined the association between metformin use and estrogen receptor status, tumour size, and lymph node status in the subset of women for whom those data were available.

**Results** We identified 3125 women with diabetes and breast cancer; 1519 (48.6%) had been exposed to metformin before their cancer diagnosis. Median age at breast cancer diagnosis was 76 years (interquartile range: 72–82 years), and mean duration of diabetes was 8.8 ± 5.9 years. In multivariable analyses, metformin exposure was not associated with an earlier stage of breast cancer (odds ratio: 0.98; 95% confidence interval: 0.81 to 1.19). In secondary analyses, metformin exposure was not associated with estrogen receptor–positive breast cancer, tumours larger than 2 cm, or positive lymph nodes.

**Conclusions** This population-based study did not show an association between metformin use and breast cancer stage or tumour characteristics at diagnosis. Our study considered older women with long-standing diabetes, and therefore further studies in younger patients could be warranted.

**Key Words** Breast cancer stage, population-based studies

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## INTRODUCTION

Diabetes is associated with an increased risk of breast cancer and a 40% higher risk of mortality after a cancer diagnosis[1]. Insulin resistance and hyperinsulinemia might predispose women with type 2 diabetes to more aggressive tumours, contributing to their higher breast cancer mortality[2]. Indeed, we previously showed that women with diabetes are more likely to present with later-stage breast cancer, even after adjusting for prior screening mammography[3].

Interventions that reduce circulating insulin might influence cancer growth and stage at diagnosis in women with diabetes who develop breast cancer. Metformin, an insulin-sensitizing medication used to treat diabetes, has been associated with reduced tumour growth[4–7] and improved pathologic complete response in breast cancer patients receiving neoadjuvant chemotherapy[8]. Furthermore, observational studies have shown a lower risk of breast[9,10] and other cancers[11,12] and lower breast cancer mortality[13] in women with diabetes treated with metformin.

It remains unknown whether treatment with metformin has an effect on tumour growth and subtype before breast cancer is diagnosed clinically. To date, no studies have examined the association between metformin and breast cancer stage. Because metformin is a common therapy for type 2 diabetes, it is important to determine whether it modifies not only the risk of breast cancer but also the stage at which the disease presents in women with diabetes.

A small study reported that, compared with non-users of metformin, users presented with less locally invasive breast cancer[14]. Similarly, a study from the U.S. Women's Health Initiative found a reduction in invasive breast cancer among metformin users[15]. Whether metformin affects molecular breast cancer subtype is controversial.

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One study reported a reduction in hormone-sensitive tumours with metformin exposure[15]; others reported either an increase[16,17] or no difference in hormone-positive tumours[14]. Those prior studies have been limited by small sample sizes, incomplete drug data, and inconsistent comparator groups and statistical methods. Furthermore, all but one accounted for screening patterns, an important predictor of stage[18]. Screening mammography rates are also influenced by comorbidities such as diabetes, which could modify the relationship between diabetes treatment and cancer stage[19].

The objective of the present study was to use a large, population-based cohort to examine the association between metformin use and breast cancer stage at diagnosis while accounting for mammography differences. We also explored the association between metformin use and tumour size, lymph node status, and hormone receptor status.

## METHODS

This retrospective population-based cohort study used data from administrative health care databases in Ontario, which include records for all individuals eligible for coverage under the province's universal health insurance plan. The various datasets were linked using unique encoded identifiers and were analyzed at the Institute for Clinical Evaluative Sciences.

### Data Sources and Population

The study cohort was identified from among the population of Ontario women with diabetes, 68 years of age or older, who were diagnosed with invasive breast cancer from 1 January 2007 to 31 December 2012. The cohort was restricted to older women so as to capture at least 3 years of prescription drug records before the cancer diagnosis. Those records are available through the Ontario Drug Benefit plan for all individuals 65 years of age and older.

We used the Ontario Cancer Registry to identify women diagnosed with invasive breast cancer. The Ontario Cancer Registry contains data for all Ontario residents who have been diagnosed with or died of cancer since 1964[20]. Individuals with any prior diagnosis of cancer (except non-melanoma skin cancer) in the Ontario Cancer Registry were excluded. We included only breast cancers diagnosed after 2007, because that was the year in which stage data became available for most breast cancers in the relevant databases.

We then used the validated Ontario Diabetes Database to identify women with diabetes. The Ontario Diabetes Database has been validated against primary care records and has high sensitivity and specificity for identifying individuals with diabetes[21]. To be included in the study cohort, a woman had to have been diagnosed with diabetes at any time before her breast cancer diagnosis. We excluded patients diagnosed with diabetes before age 30, because those women might have been affected by type 1 diabetes.

The Discharge Abstract Database maintained by the Canadian Institute for Health Information and the Ontario Health Insurance Plan database provided information about physician service claims. We used the Ontario Breast Screening Program database to look for mammography history. The National Ambulatory Care Reporting System was used to identify patients on dialysis and those with chronic renal failure. We obtained information on demographics and deaths from the Registered Persons Database. Records from these administrative health care databases were linked anonymously using encrypted health card numbers.

### Outcomes

Our primary outcome was breast cancer stage at time of diagnosis based on Cancer Care Ontario's cancer stage data. Patients were classified as having stage I, II, III, or IV breast cancer. Collaborative stage was determined if available; otherwise, we used stage data supplied by regional cancer centres. Our secondary outcomes were estrogen receptor status (positive, negative, unknown), tumour size (<2 cm or ≥2 cm), and lymph node status (positive, negative, unknown).

#### *Primary Exposure*

Metformin use was the main exposure of interest. For a woman to be categorized as a metformin user, she had to fill at least 2 consecutive scrips for metformin at any point in the 3-year period preceding her breast cancer diagnosis. Two scrips were considered to be consecutive if the second scrip was filled within an interval no longer than the duration of the previous prescription, plus a grace period of up to 50%.

For the primary analysis, metformin use was categorized as a binary exposure, where the comparator group consisted of non-users of metformin. Non-users of metformin included women prescribed either another oral glucose-lowering agent (sulfonylurea, thiazolidinedione, glucagon-like peptide 1, other) or insulin, or women receiving no pharmacotherapy. We also calculated each metformin user's cumulative exposure to metformin from age 65 by summing the number of days during which they were prescribed metformin (even if the days were non-consecutive) before their breast cancer diagnosis date. We categorized exposure into less than 1 year, 1–3 years, and more than 3 years of cumulative metformin exposure.

#### *Other Covariates*

Income status was based on neighborhood income quintile, derived from census data linked to postal codes in the Registered Persons Database. Rural compared with urban status was determined by linking postal codes to census data. Specific comorbidities were determined at baseline (derived from the Discharge Abstract Database and the National Ambulatory Care Reporting System). An overall comorbidity score was estimated using the Johns Hopkins Adjusted Clinical Group case mix. The Adjusted Clinical Group weighted case-mix score has been shown to predict mortality in ambulatory settings for patients with diabetes in Ontario[22].

We also recorded health care variables. Number of visits to the primary care physician in the 2 years preceding diagnosis was obtained from Ontario Health Insurance Plan records. Receipt of mammography within 3 years before, but no less than 60 days before, the breast cancer diagnosis was determined using Ontario Health Insurance

Plan billing claims and the Ontario Breast Screening Program database. We limited the period to no less than 60 days before the breast cancer diagnosis to capture mammography that would most likely have been performed for screening rather than for diagnostic purposes.

### Statistical Analyses

Baseline variables are described using summary statistics. Univariate and adjusted logistic regression models were used to compare breast cancer stage at diagnosis for women exposed and not exposed to metformin. The analyses compared the likelihood of presenting with stage I or II or with stage III or IV disease. Covariates that were statistically significant in the univariate models or those known to be clinically relevant were included in the multivariable model. The multivariable model was adjusted for age at breast cancer diagnosis, neighbourhood income quintile, urban residence (yes or no), number of outpatient visits in the 2 years preceding the breast cancer diagnosis, the Johns Hopkins Aggregated Diagnosis Groups weighted score, diabetes duration (years), use of other oral hypoglycemic agents (yes or no), use of insulin (yes or no), and mammography within 3 years of the breast cancer diagnosis.

### Secondary Analyses

For secondary outcomes, we examined the association between metformin use and estrogen receptor status (positive vs. negative or unknown), tumour size (<2 cm vs. ≥2 cm), and positive lymph node status in the subset of women diagnosed with breast cancer during 2010–2012 for whom those data were available.

To examine the effect of various patterns of metformin use on the outcomes of interest, we categorized metformin use into current and past use. "Current use" was accepted if the two consecutive scrips overlapped with the 180 days before the breast cancer diagnosis. "Past use" was accepted if 2 or more consecutive scrips for metformin were filled more than 180 days before the breast cancer diagnosis. To isolate metformin's effect from that of insulin or other glucose-lowering agents, we performed these additional subgroup analyses: insulin users excluded; metformin monotherapy users compared with non-users of metformin; and metformin monotherapy users compared with women taking no glucose-lowering agents.

We also conducted two sets of pre-specified subgroup analyses. First, we stratified the cohort by diabetes duration (<2 years, 2–5 years, >5 years). Second, to account for total drug exposure, we stratified the cohort by age of diabetes diagnosis (<65 years, ≥65 years), thus capturing complete drug exposure for individuals more than 65 years of age at time of diabetes diagnosis.

This study was approved by the institutional review board at Sunnybrook Health Sciences Centre, Toronto, Ontario.

## RESULTS

The study population consisted of 3125 women with diabetes and breast cancer, among whom 1519 (48.6%) were exposed to metformin before their breast cancer diagnosis. Median age at breast cancer diagnosis was 76 years (interquartile range: 72–82 years), and mean duration of diabetes before breast cancer diagnosis was 8.8 ± 5.9 years.

Table I presents baseline variables by exposure to metformin. Users of metformin were slightly younger at breast cancer diagnosis and had a longer duration of diabetes. Non-users had a higher prevalence of chronic renal failure, but the two groups had similar proportions of other comorbidities. The mean duration of metformin use was 2.3 ± 0.9 years. Among users of metformin, 636 (41.9%) were exposed to sulfonylureas, 189 (12.4%) to thiazolidinediones, 216 (14.2%) to insulin, 53 (3.5%) to DPP-4 inhibitors, and 25 (1.7%) to acarbose during the 3 years before their cancer diagnosis.

In multivariable analyses, metformin exposure before breast cancer, compared with no exposure, was not associated with an earlier stage of breast cancer at diagnosis [odds ratio (OR): 0.98; 95% confidence interval (CI): 0.81 to 1.19]. Similarly, no association between cumulative metformin dose and stage at diagnosis was observed (Table II).

### Secondary Outcomes

For the subset of women with available data about receptor status, tumour size, and lymph node status, we compared the likelihood of those outcomes in women using and not using metformin. Comparing users of metformin with non-users, we observed no differences in the likelihood of presenting with estrogen receptor–positive breast cancer (OR: 0.97; 95% CI: 0.73 to 1.29), with a tumour 2 cm or larger (OR: 1.15; 95% CI: 0.92 to 1.44), or with positive lymph nodes (OR: 0.95; 95% CI: 0.75 to 1.19; Table III).

When women with metformin exposure were classified into current and past users, no difference in stage at presentation was observed for either group compared with the non-users of metformin (current-use OR: 1.06; 95% CI: 0.86 to 1.31; past-use OR: 0.82; 95% CI: 0.62 to 1.07). Similarly, when women with metformin exposure were further categorized into metformin monotherapy users, stage at presentation was not difference for those women compared with non-users of metformin or with women not on any pharmacotherapy (Table IV).

In the subgroup analyses, we observed no associations of metformin use with breast cancer stage by category of diabetes duration or for women more than 65 years of age at the time of breast cancer diagnosis [a group for whom all metformin exposure could be accounted for (results not shown)].

## DISCUSSION

Our large population-based study failed to show an effect of metformin treatment on the stage or type of tumours in older women with diabetes who present with breast cancer. After adjustment for prior mammography screening, age, health care visits, comorbidity, and income, no association between metformin exposure and breast cancer stage, hormone receptor status, tumour size, or lymph node status at diagnosis was evident. Those findings suggest that metformin, when used to treat diabetes, does not influence breast tumour characteristics in the preclinical period for older women diagnosed with breast cancer.

**TABLE I** Baseline characteristics of women with diabetes exposed and not exposed to metformin before a breast cancer diagnosis

| Characteristic | Metformin exposure[a] | | |
|---|---|---|---|
| | Overall | Yes | No |
| Patients (*n*) | 3125 | 1519 | 1606 |
| Age at cancer diagnosis (years) | | | |
| Median | 76 | 75 | 77 |
| Interquartile range | 72–82 | 71–81 | 72–83 |
| Mean duration (years) | | | |
| Of diabetes | 8.8±5.9 | 10.0±5.6 | 7.5±5.9 |
| Of metformin use | 2.3±0.9 | 2.3±0.9 | — |
| Metformin duration group [*n* (%)] | | | |
| <1 Year | | 190 (12.5) | — |
| 1–3 Years | | 1027 (67.6) | — |
| >3 Years | | 302 (19.9) | — |
| Exposure to other glucose-lowering medications [*n* (%)] | 1185 (37.9) | 803 (52.9) | 382 (23.8) |
| Sulfonylurea | 830 (26.6) | 636 (41.9) | 194 (12.1) |
| Thiazolidinedione | 228 (7.3) | 189 (12.4) | 39 (2.4) |
| DDP4 inhibitors | 59 (1.9) | 53 (3.5) | 6 (0.4) |
| Insulin | 407 (13.0) | 216 (14.2) | 191 (11.9) |
| Comorbidities [*n* (%)] | | | |
| Stroke | 58 (1.9) | 33 (2.2) | 25 (1.6) |
| Myocardial infarction | 149 (4.8) | 69 (4.5) | 80 (5.0) |
| Congestive heart failure | 197 (6.3) | 98 (6.5) | 99 (6.2) |
| Chronic renal failure | 252 (8.1) | 102 (6.7) | 150 (9.3) |
| Diabetic complications | 370 (11.8) | 175 (11.5) | 195 (12.1) |
| Mean ADG score | 19.4±13.1 | 19.4±13.2 | 19.5±13.0 |
| Screening mammography [*n* (%)] | 1495 (47.8) | 726 (47.8) | 769 (47.9) |
| Neighbourhood income quintile [*n* (%)] | | | |
| 1 | 716 (22.9) | 375 (24.7) | 341 (21.2) |
| 2 | 704 (22.5) | 364 (24.0) | 340 (21.2) |
| 3 | 579 (18.5) | 264 (17.4) | 315 (19.6) |
| 4 | 591 (18.9) | 282 (18.6) | 309 (19.2) |
| 5 | 524 (16.8) | 229 (15.1) | 295 (18.4) |

[a] Defined as filling at least 2 consecutive scrips for metformin at any point in the 3-year period preceding breast cancer diagnosis.
DDP4 = dipeptidyl peptidase-4; ADG = Johns Hopkins Aggregated Diagnosis Groups.

**TABLE II** Unadjusted and adjusted logistic regression models estimating the risk of advanced stage of breast cancer (I, II vs. III, IV) in women with and without metformin exposure

| Variable | Unadjusted analysis | | Adjusted analysis[a] | |
|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI |
| Metformin use | 0.94 | 0.79 to 1.12 | 0.98 | 0.81 to 1.19 |
| Cumulative metformin duration | | | | |
| <1 Year | 1.06 | 0.72 to 1.54 | 1.13 | 0.76 to 1.67 |
| 1 to 3 Years | 0.88 | 0.73 to 1.06 | 0.92 | 0.75 to 1.13 |
| >3 Years | 1.13 | 0.83 to 1.55 | 1.15 | 0.82 to 1.61 |

[a] Model adjusted for age at breast cancer diagnosis, socioeconomic status, urban residence (yes or no), number of outpatient visits in the 2 years preceding the breast cancer diagnosis, aggregated diagnosis group weighted score, diabetes duration (years), use of other oral hypoglycemic agents (yes or no), use of insulin (yes or no), mammogram within the 3 years preceding the breast cancer diagnosis.
OR = odds ratio; CI = confidence interval.

**TABLE III** Adjusted logistic regression model[a] estimating the effect of metformin use on estrogen receptor status, tumour size, and lymph node status

| Variable | Adjusted analysis, metformin users | |
|---|---|---|
| | OR | 95% CI |
| Estrogen receptor positivity | 0.97 | 0.73 to 1.29 |
| Tumour size greater than 2 cm | 1.15 | 0.92 to 1.44 |
| Lymph node positivity | 0.95 | 0.75 to 1.19 |

[a] Model adjusted for age at breast cancer diagnosis, socioeconomic status, urban residence (yes or no), number of outpatient visits in the 2 years preceding the breast cancer diagnosis, aggregated diagnosis group weighted score, diabetes duration (years), use of other oral hypoglycemic agents (yes or no), use of insulin (yes or no), mammogram within the 3 years preceding the breast cancer diagnosis.

OR = odds ratio; CI = confidence interval.

**TABLE IV** Adjusted logistic regression models estimating the effect of metformin on breast cancer stage (I, II vs. III, IV), subgroup analyses by metformin exposure

| Variable | Adjusted analysis, metformin users | |
|---|---|---|
| | OR | 95% CI |
| Any metformin use | | |
| Current[a] | 1.06 | 0.86 to 1.31 |
| Past[a] | 0.82 | 0.62 to 1.07 |
| Excluding insulin users[b] | 0.96 | 0.78 to 1.18 |
| Metformin monotherapy | | |
| Versus no metformin[a] | 1.00 | 0.78 to 1.27 |
| Versus other oral agents[c] | 1.05 | 0.70 to 1.57 |

[a] Adjusted for age at breast cancer diagnosis, socioeconomic status, urban residence (yes or no), number of outpatient visits in the 2 years preceding the breast cancer diagnosis, aggregated diagnosis group weighted score, diabetes duration (years), use of other oral hypoglycemic agents (yes or no), use of insulin (yes or no), mammogram within the 3 years preceding the breast cancer diagnosis.

[b] Adjusted for age at breast cancer diagnosis, socioeconomic status, urban residence (yes or no), number of outpatient visits in the 2 years preceding the breast cancer diagnosis, aggregated diagnosis group weighted score, diabetes duration (years), use of other oral hypoglycemic agents (yes or no), mammogram within the 3 years preceding the breast cancer diagnosis.

[c] Adjusted for age at breast cancer diagnosis, socioeconomic status, urban residence (yes or no), number of outpatient visits in the 2 years preceding the breast cancer diagnosis, aggregated diagnosis group weighted score, diabetes duration (years), mammogram within the 3 years preceding the breast cancer diagnosis.

To our knowledge, the present study is the first to examine the association between metformin and breast cancer stage in women with diabetes. Furthermore, it is the largest study to date to examine the relationship between metformin and tumour characteristics and subtypes. Earlier studies were small, and most did not account for diabetes duration, comorbidities, or prior screening mammography. Furthermore, outcomes and methods varied from study to study.

In an analysis of 253 women, metformin users had a lower proportion of locally invasive disease; however, no difference was reported in tumour size, hormone receptor status, or lymph node positivity[14]. A smaller study of 90 women with diabetes and breast cancer reported an increased frequency of progesterone receptor–positive breast tumours among metformin users[16]. Finally, a study from the U.S. Women's Health Initiative found that metformin users were less likely to present with invasive breast cancer; however, the authors did not explore the relationship between metformin and breast cancer stage[15].

There is evidence that metformin has antitumour properties. In preclinical studies, metformin was found to inhibit tumour spread and to reduce tumour growth[23,24]. In short-term window-of-opportunity studies, metformin was shown to affect tumour growth both through indirect, insulin-dependent pathways[6,7,25] and by activating AMPK pathways to directly affect cancer cells[26,27]. However, in larger epidemiologic studies, those actions have not translated into an improvement in tumour stage or cancer burden for either breast cancer or other cancers. A study examining the effect of metformin exposure on colorectal cancer at presentation found that there was no difference in the risk of disseminated disease between users and non-users of metformin[28]. That result might be due to the fact that, in epidemiologic studies, "metformin users" often includes patients on insulin, the presence of which could be negating any effect of metformin. However, our study failed to support that possibility: results were similar when insulin users were excluded. Furthermore, there is evidence that metformin is associated with a greater reduction in tumour growth in individuals who attain the largest reduction in insulin level[29]. Thus, metformin's effect might be lost when not accounting for varying levels of insulin resistance.

In previous work, we showed that metformin use after a breast cancer diagnosis is not associated with decreased all-cause mortality[13]. Although metformin use was associated with lower breast cancer–specific mortality, our results did not reach statistical significance. In the present study, we explored whether metformin might affect tumour growth during the preclinical stages of breast cancer. Although our results are null, our study population was limited to older women diagnosed with breast cancer after the age of 68. Metformin might have a different effect in women who are younger at time of their cancer and diabetes diagnoses, and thus further studies could be warranted in those populations.

There are many strengths to the present study. It is the first study to use a large population-based cohort to determine the effect of metformin on breast cancer stage. We had access to validated databases for defining breast cancer and diabetes patients, and comprehensive stage data on a large proportion of the cohort. We also had universal drug data and were able to identify a minimum of 3 years of drug exposure in the study population. Moreover, we were able to account for mammography use. There are, however, limitations to the study. Clinical data—that is, body mass index, HbA1c, family history, and so on—were not available, and thus we could not adjust for those variables. We had to exclude 775 breast cancer patients because of missing stage data, which might have affected the generalizability of our results. Finally, we were limited to drug exposure that occurred after age 65, and thus the results might not be generalizable to younger patients.

## CONCLUSIONS

This population-based study did not show an association between metformin exposure and breast cancer stage or tumour characteristics at diagnosis. The null association remained even when accounting for long-term metformin use, as well as for differing durations of diabetes. Those findings fail to support a role for metformin in breast tumour growth in the preclinical stage. Our study considered older women with long-standing diabetes, and therefore further studies in younger patients could be warranted.

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### CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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