Long-Term Metformin Use Is Associated With Decreased Risk of Breast Cancer

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OBJECTIVE — To evaluate whether use of oral hypoglycemic agents is associated with an altered breast cancer risk in women.

RESEARCH DESIGN AND METHODS — Using the U.K.-based General Practice Research Database, we conducted a nested case-control analysis among 22,621 female users of oral antidiabetes drugs with type 2 diabetes. We evaluated whether they had an altered risk of breast cancer in relation to use of various types of oral hypoglycemic agents. Case and control patients with a recorded diagnosis of type 2 diabetes were matched on age, calendar time, and general practice, and the multivariate conditional logistic regression analyses were further adjusted for use of oral antidiabetes drugs, insulin, estrogens, smoking BMI, diabetes duration, and HbA1c (A1C).

RESULTS — We identified 305 case patients with a recorded incident diagnosis of breast cancer. The mean ± SD age was 67.5 ± 10.5 years at the time of the cancer diagnosis. Long-term use of ≥40 prescriptions (>5 years) of metformin, based on 17 exposed case patients and 120 exposed control patients, was associated with an adjusted odds ratio of 0.44 (95% CI 0.24–0.82) for developing breast cancer compared with no use of metformin. Neither short-term metformin use nor use of sulfonylureas or other antidiabetes drugs was associated with a materially altered risk for breast cancer.

CONCLUSIONS — A decreased risk of breast cancer was observed in female patients with type 2 diabetes using metformin on a long-term basis.

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Type 2 diabetes has been related to an elevated risk of various cancer types. Many studies have indicated that diabetes is associated with a modestly increased risk of postmenopausal breast cancer (1), although some authors found no such association, as discussed in detail by Xue and Michels (1).

Type 2 diabetes is characterized by insulin resistance and hyperinsulinemia. Aside from its metabolic effects, insulin also has mitogenic effects that are mediated through the IGF-I receptor and insulin receptor (2). Epidemiological studies have demonstrated that insulin resistance and hyperinsulinemia are related to an increased risk of epithelial malignancy, including breast, prostate, colon, and kidney (2,3). It was shown that higher levels of fasting insulin in women without diabetes were associated with an increased risk of breast cancer development (4). Furthermore, diabetes was associated with markedly increased mortality in women with breast cancer (5). Therefore, improving insulin resistance and correcting hyperinsulinemia may be an effective strategy to reduce both the risk of developing breast cancer and the risk of breast cancer-related mortality.

Metformin is known to improve hyperinsulinemia and insulin resistance mainly by decreasing hepatic gluconeogenesis and increasing glucose disposal in muscle. Use of metformin was associated with a decreased risk of cancer in patients with type 2 diabetes in various observational studies; however, the authors did not provide detailed information on the risk of breast cancer (6,7). In another epidemiological study, users of metformin had significantly decreased cancer-related mortality compared with users of either sulfonylureas or insulin (8). Recently, Currie et al. (9) observed no alteration of breast cancer risk in association with metformin use in a subgroup analysis in their retrospective cohort study. Female diabetic patients receiving neoadjuvant chemotherapy for breast cancer were reported to have a higher complete pathologic response rate if they also used metformin compared with those not using metformin (10). Recently, Landman et al. (11) reported a lower cancer-related mortality for metformin users compared with that for nonusers. Anisimov et al. (12) showed that metformin increased the life span and decreased development of spontaneous mammary tumors in HER-2/neu transgenic mice. Further work in breast cancer cells demonstrated that metformin does not act as an "insulin-sensitizing" drug, but as a growth inhibitor; growth inhibition was mediated by upregulation of AMP-activated protein kinase (AMPK) activity and downstream suppression of signaling through the mammalian target of rapamycin (13,14). These studies suggest that metformin exerts direct antitumor activity mainly by activation of AMPK and consequently interferes with cancer cell metabolism.

To date, there is only sparse evidence from epidemiological studies addressing the association between metformin and the risk of breast cancer. Because breast cancer is a frequently diagnosed cancer and because the studies mentioned above suggest a probable effect of metformin on breast cancer development and growth, we conducted a case-control analysis to explore the association between long-term use of metformin and other hypogly-

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cemic agents and the risk of developing breast cancer.

RESEARCH DESIGN AND METHODS

— Data were derived from the U.K.-based General Practice Research Database (GPRD) (15). In brief, this database was established around 1987 and currently encompasses some 5 million people who are enrolled with selected general practitioners, covering ~50 million person-years of follow-up. The patients enrolled in the GPRD are representative of the U.K. with regard to age, sex, geographic distribution, and annual turnover rate. General practitioners have been trained to record medical information including demographic data, medical diagnoses, hospitalizations, deaths, and drug prescriptions using standard software and standard coding systems. The general practitioners generate prescriptions directly with the computer, and this information is automatically transcribed into the computer record. It contains the name of the preparation, instructions for use, route of administration, dose, and number of tablets for each prescription. The recorded information on drug exposure and diagnoses has been validated and proven to be of high quality (16). The GPRD has been the source of many observational studies, including research on diabetes and antidiabetes drugs (17–19) and on cancer (20). The study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research.

We first identified all subjects in the GPRD who had a diabetes diagnosis and/or who received at least one prescription for an oral hypoglycemic drug including sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, or prandial glucose regulators, with or without concomitant insulin use, and who were between the ages of 30 and 79 years between 1994 and 2005. Diabetic patients who received only insulin were not included. We excluded all patients with <3 years of recorded history in the database before the date of the first diabetes diagnosis or the first prescription for an antidiabetes drug (whichever came first), as well as all patients with alcoholism and women with a diagnosis of gestational diabetes at any time in their record.

Within this diabetic study population aged 30–79 years, we then identified all women followed up to 89 years of age who had, after the first prescription for an oral antidiabetes drug, a recorded first-time diagnosis of either invasive breast cancer or carcinoma in situ which was followed by breast surgery, radiation, chemotherapy, antiestrogen therapy (tamoxifen or anastrazole), or a combination thereof. The date of this first diagnosis of interest will be referred to as the "index date."

Within the study population we identified at random up to four control patients per breast cancer case patient, matched to case patients on age (same year of birth), sex, general practice, and index date (i.e., the control patient got the same index date assigned, i.e., the date of the first-time recorded cancer diagnosis of the case patient). The aim of matching for index date was to compare drug exposure between case and control patients at the same point in time to avoid confounding by calendar time.

As with the case patients, control patients also had to have their first exposure to an oral antidiabetes drug recorded before the index date, and they also had to be free of any cancer diagnosis before the index date.

Statistical analysis

We conducted a nested case-control analysis, whereby we assessed exposure to oral antidiabetes drugs and insulin from the computer records before the index date in case and control patients. We classified users of antidiabetes drugs according to the drug class (insulin, sulfonylureas, metformin, thiazolidinediones, prandial glucose regulators, or α-glucosidase inhibitors) and the duration of use, based on the number of prescriptions received (none, 1–9, 10–39, or ≥40 prescriptions). Based on the average number of tablets per prescription, the category of ≥40 prescriptions reflects an exposure duration of ~≥5 years. We conducted conditional logistic regression analyses using SAS 9.1 (SAS Institute, Cary, NC) to compare the exposure prevalence between cancer case patients and control patients. Risk estimates are presented as odds ratios (ORs) with 95% CIs. *P* values are two-sided and considered statistically significant if $P < 0.05$. We compared metformin users with nonusers of metformin (including users of the other oral hypoglycemic drugs) and adjusted the multivariate model for use of sulfonylureas, thiazolidinediones, insulin, and other oral antidiabetes drugs to evaluate whether an alteration of the OR for breast cancer among metformin users may be confounded by use of other oral antidiabetes drugs. We also evaluated duration of use of oral antidiabetes drugs, comparing each level of duration with nonusers of the respective drug class. We further adjusted the model for smoking status (none, current, past, and unknown), BMI (<25, 25–29.9, and ≥30 kg/m^2), duration of diabetes (<1 year, 1–2 years, and >2 years), and the last reported A1C level (<6.5%, 6.5–7.4%, 7.5–8.9%, and ≥9%) before the index date as well as for use of postmenopausal estrogens (none, 1–19, and ≥20 prescriptions). We also assessed whether case and control patients had renal failure, congestive heart failure, ischemic heart disease, stroke/transient ischemia attack, hypotension, hypertension, or dyslipidemia and explored whether these diseases confounded the association between use of oral antidiabetes drugs and the risk of breast cancer, both in univariate models and in the final multivariate model. For this purpose, we included potential confounders one by one in the model to see whether they altered the main association of interest, i.e., use of antidiabetes drugs and the risk of developing breast cancer. Because none of these parameters materially altered the OR of developing breast cancer, we did not include them in the final model. We further assessed use of aspirin, tamoxifen, or raloxifene as well as the number of breast biopsies recorded before the index date. Because these parameters also did not alter the OR in the multivariate analysis, we did not include them in the final model.

RESULTS

— The study population encompassed 22,621 women who received at least one prescription for at least one study drug. Within this study population, we identified 305 case patients with a recorded incident diagnosis of breast cancer who fulfilled our inclusion criteria, with a mean ± SD age of 67.5 ± 10.5 years at the time of the cancer diagnosis. The matched control sample encompassed 1,153 cancer-free women. Thus, we had 3.8 control patients per case patient on average and 266 of 305 (87%) sets had a full 4:1 match. Characteristics of case and control patients are displayed in Table 1, and Table 2 presents detailed data about the various antidiabetes drug combinations used by case and control patients.

Overall, the OR for any versus no metformin use was 1.03 (95% CI 0.76–1.39), adjusted for use of insulin, sulfonylureas, thiazolidinediones, prandial

Table 1—*Characteristics of female breast cancer case patients and their control patients*

	Case patients	Control patients	Crude OR (95% CI)*
n	305	1,153	
Age (years)			
<40	5 (1.6)	7 (0.6)	—
40–49	14 (4.6)	57 (4.9)	—
50–59	40 (13.1)	167 (14.5)	—
60–69	99 (32.5)	359 (31.2)	—
70–79	113 (37.0)	445 (38.6)	—
≥80	34 (11.2)	118 (10.2)	—
BMI (kg/m^2)			
<25	48 (15.7)	174 (15.1)	1.00 (referent)
25–30	100 (32.8)	356 (30.9)	1.01 (0.68–1.48)
≥30	138 (45.3)	526 (45.6)	0.95 (0.65–1.38)
Unknown	19 (6.2)	97 (8.4)	0.69 (0.38–1.27)
Smoking status			
Nonsmoker	190 (62.3)	677 (58.7)	1.00 (referent)
Current	32 (10.5)	168 (14.6)	0.71 (0.47–1.07)
Past	71 (23.3)	245 (21.2)	1.08 (0.78–1.48)
Unknown	12 (3.9)	63 (5.5)	0.66 (0.33–1.31)
Estrogen use			
Nonuser	220 (72.1)	902 (78.2)	1.00 (referent)
1–19 prescriptions	49 (16.1)	174 (15.1)	1.18 (0.82–1.70)
≥20 prescriptions	36 (11.8)	77 (6.7)	2.10 (1.34–3.28)
Diabetes history (years)			
<1	57 (18.7)	216 (18.7)	1.00 (referent)
1–2	55 (18.0)	194 (16.8)	1.14 (0.74–1.76)
≥2	193 (63.3)	743 (64.5)	1.07 (0.74–1.54)
A1C (%)			
<6.5	69 (22.6)	239 (20.7)	1.00 (referent)
6.5–7.4	72 (23.6)	275 (23.9)	0.91 (0.62–1.33)
7.5–8.9	62 (20.4)	233 (20.2)	0.92 (0.62–1.39)
≥9	51 (16.7)	187 (16.2)	0.89 (0.58–1.38)
Unknown	51 (16.7)	219 (19.0)	0.68 (0.42–1.10)
Renal failure	10 (3.0)	43 (3.7)	0.78 (0.38–1.63)
Congestive heart failure	15 (4.9)	88 (7.6)	0.65 (0.37–1.14)
Ischemic heart disease	60 (19.7)	218 (18.9)	1.09 (0.78–1.52)

Data are *n* (%) unless otherwise indicated. *Adjusted for age, sex, general practice, and calendar time by matching.

glucose regulators, acarbose, smoking BMI, use of postmenopausal estrogens, diabetes duration, and A1C level. When we stratified metformin use by exposure duration, use of short duration was not associated with a materially altered OR, whereas long-term use of metformin, defined as ≥30 prescriptions, was associated with an adjusted OR of 0.63 (0.39–1.00) for developing breast cancer, based on 33 case patients and their control patients compared with nonuse. If we defined long-term use of metformin as ≥40 prescriptions, the adjusted OR was 0.44 (0.24–0.82, $P = 0.01$), based on 17 case patients and their control patients compared with nonuse of metformin (Table 3). Further adjustment for congestive heart failure, ischemic heart disease, or renal failure did not modify the OR of interest (data not shown). The OR for long-term use (≥20 prescriptions before the index date) of estrogens in the multivariate model was 2.22 (1.38–3.55), adjusted for use of metformin, use of other antidiabetes drugs BMI, smoking, diabetes duration, and A1C. Neither short- nor long-term use of sulfonylureas was associated with an altered OR of breast cancer (adjusted OR 1.03, 95% CI 0.62–1.70 for users of ≥40 prescriptions) in this multivariate model (Table 3).

In an additional analysis, we assessed the effect of oral antidiabetes drugs on the OR of developing breast cancer after excluding all insulin users. The adjusted OR for users of ≥40 metformin prescriptions compared with nonusers of metformin was 0.42 (95% CI 0.21–0.87, $P = 0.02$), whereas it remained virtually unaltered for users of other oral antidiabetes drugs (Table 4).

CONCLUSIONS — In this observational study in a population of women with type 2 diabetes, we found a decreased risk of breast cancer in women who used metformin for several years, whereas no such effect was seen for short-term use. The association was similar when we removed insulin users from the analysis. In a previous observational study of 983 cancers, Evans et al. (6) reported an overall decreased risk of cancer for metformin users (>31 prescriptions, adjusted OR 0.73, 95% CI 0.56–0.94). However, the authors did not provide data stratified by individual cancer types, nor did they report whether use of insulin was excluded or controlled for in their analyses (6). Libby et al. (7) reported an adjusted hazard ratio (HR) for cancer of 0.63 (95% CI 0.53–0.75) in patients with type 2 diabetes in metformin users versus nonusers of this drug. Again, no specific information on the breast cancer risk was available. In a similar study, Currie et al. (9) observed that metformin monotherapy carried the lowest risk of cancer among patients with type 2 diabetes; however, they found no risk alteration in breast cancer patients using metformin. In another population-based study using administrative data from Saskatchewan, Bowker et al. (8) found an increased cancer-related mortality for patients with type 2 diabetes who used sulfonylureas (adjusted HR 1.3, 95% CI 1.1–1.6) or insulin compared with metformin users.

Several clinical studies in pre- and postmenopausal women with (1) or without (21) type 2 diabetes revealed a significantly higher risk of breast cancer in association with hyperinsulinemia and insulin resistance. Furthermore, high fasting insulin levels and obesity have been associated with poor cancer-related outcome (4). Both the reduction of hyperinsulinemia and growth inhibition via AMPK activation might explain why metformin therapy seems to be associated with a decreased risk of breast cancer. This has been hypothesized by various authors (22,23) and is supported by the current findings.

Thiazolidinediones, like metformin, are known to correct hyperinsulinemia and insulin resistance, and their use may also be associated with diminished breast cancer development or growth. In our

Table 2—*Antidiabetic drug utilization among breast cancer cases and control patients*

Antidiabetic drug use	Case patients	Control patients
n	305	1,153
None	68 (22.3)	255 (22.1)
Insulin only	0 (0)	2 (0.1)
Sulfonylureas only	64 (21.0)	250 (21.7)
Metformin only	62 (20.3)	198 (17.3)
Insulin and sulfonylureas	7 (2.3)	25 (2.2)
Insulin and metformin	4 (1.3)	22 (1.9)
Sulfonylureas and metformin	55 (18.1)	263 (22.8)
Insulin, sulfonylureas, and metformin	23 (7.5)	64 (5.5)
Other*	22 (7.2)	74 (6.4)

Data are *n* (%). *Any combination of the above drugs with a thiazolidinedione, acarbose, or a prandial glucose regulator.

study, the number of patients exposed to thiazolidinediones was too small to allow robust analyses. There was, however, a tendency toward an increased relative breast cancer risks for long-term users (≥10 prescriptions) of thiazolidinediones, but the finding did not reach statistical significance. A possible association between use of thiazolidinediones and an altered risk of cancer has recently been described (24). The authors reported a 33% reduction in lung cancer risk among users of thiazolidinediones compared with nonusers (for whites, adjusted HR 0.74, 95% CI 0.58–0.95). However, they did not report whether they also assessed metformin use and breast cancer risk.

There are several limitations in our study that need to be acknowledged. First, there may be some misclassification of cancer diagnoses because we did not send for medical records for breast cancer case patients to get a final confirmation of the cancer, e.g., via histology. However, the GPRD has been used numerous times for studying cancer, and previous validation studies provided convincing evidence that most cancer diagnoses are recorded with high validity in the GPRD (>90%) (20). Furthermore, we assessed a random sample of case report forms and verified the validity of our inclusion criteria as explained in RESEARCH DESIGN AND METHODS. In addition, any misclassification would probably have occurred at random and would not be associated with use of a particular oral antidiabetes drug such as metformin. Second, although we analyzed a large number of patients with breast cancer, we were not in a position to differentiate them according to standards in clinical oncology because of a lack of information about staging, histology, and molecular biology of these tumors. Third, we lacked some clinical information on glycemic control (e.g., detailed reports on blood glucose levels) as well as risk factors such as physical activity or nutritional habits. However, we assessed both duration of diabetes and level of A1C and important complications of diabetes (e.g., ischemic heart disease, stroke, and renal failure), but all of these variables did not alter the OR for breast cancer either in the univariate or in the multivariate model. Fourth, because of the lack of reliably recorded data, we could not assess age at menarche, age at first birth, parity, and family history of breast cancer. Although all of these are known to be associated with an altered breast cancer risk, it is highly unlikely that these parameters are associated with the type of oral antidiabetes drug used by a women later in life and therefore confounded the main association of interest. Furthermore, we could not assess the risk of breast cancer in association with use of antihyperglycemic agents across different ethnicities, because this information is not routinely available. Fifth, our conclusions are mainly based on the subgroup of 17 long-term metformin users and 120 control patients, relying, although statistically significant, on a relatively small number of case and control patients. However, we did not observe a similar effect among long-term users of other oral antidiabetes drugs, and we think that our finding may be biologically reasonable because cancer development may not be significantly impaired by short-term drug use.

In conclusion, our observational study provides evidence that long-term use of metformin may be related to decreased breast cancer risk. However, limited by the observational study design, a conclusion of association by causality cannot be drawn. Our findings add to the increasing body of evidence and may help

Table 3—*Breast cancer risk in users of oral antidiabetic drugs and users of insulin*

Drug and no. prescriptions	Case patients	Control patients	Unadjusted OR (95% CI)*	Adjusted OR (95% CI)†	*P* value‡
n	305	1,153			
Metformin					
None	140	540	1.00 (referent)	1.00 (referent)	
1–9	64	205	1.21 (0.86–1.72)	1.20 (0.82–1.78)	0.35
10–39	84	288	1.16 (0.85–1.60)	1.09 (0.76–1.55)	0.65
≥40	17	120	0.55 (0.31–0.97)	0.44 (0.24–0.82)	0.01
Sulfonylureas					
None	138	492	1.00 (referent)	1.00 (referent)	
1–9	62	243	0.87 (0.61–1.23)	0.85 (0.58–1.24)	0.39
10–39	71	292	0.87 (0.62–1.20)	0.79 (0.55–1.15)	0.22
≥40	34	126	0.96 (0.62–1.49)	1.03 (0.62–1.69)	0.92
Thiazolidinediones					
none	285	1,084	1.00 (referent)	1.00 (referent)	
1–4	4	24			
5–9	4	15			
≥10	12	30	1.59 (0.80–3.17)	1.76 (0.84–3.68)	0.13
Insulin					
none	262	1,022	1.00 (referent)	1.00 (referent)	
1–9	18	49	1.51 (0.86–2.66)	1.74 (0.95–3.21)	0.07
10–29	11	40	1.13 (0.57–2.26)	1.30 (0.62–2.70)	0.49
≥30	14	42	1.35 (0.72–2.54)	1.51 (0.76–3.01)	0.24

Data are n unless otherwise indicated. *Adjusted for age, sex, general practice, and calendar time by matching. †Adjusted for age, sex, general practice, and calendar time by matching and further adjusted for each other plus use of prandial glucose regulators, acarbose, estrogens, smoking, BMI, diabetes duration, and A1C ‡*P* values relate to the adjusted model.

Table 4—*Breast cancer risk in users of oral antidiabetic drugs excluding insulin users*

Drug and prescriptions	Case patients	Control patients	Adjusted OR (95% CI)*	*P* value
n	262	1,022		
Metformin				
None	132	509	1.00 (referent)	—
1–9	55	172	1.40 (0.94–2.09)	0.10
10–39	64	253	0.97 (0.67–1.42)	0.89
≥40	11	88	0.42 (0.21–0.87)	0.02
Sulfonylureas				
None	132	468	1.00 (referent)	—
1–9	49	208	0.90 (0.61–1.32)	0.58
10–39	54	241	0.84 (0.57–1.24)	0.38
≥40	27	105	1.11 (0.65–1.88)	0.70

Data are *n* unless otherwise indicated. *Adjusted for age, sex, general practice, and calendar time by matching and further adjusted for each other plus use of prandial glucose regulators, acarbose, thiazolidinediones, estrogens, smoking, BMI, diabetes duration, and A1C.

justify the initiation of clinical trials evaluating metformin in patients with hyperinsulinemia (e.g., type 2 diabetes) and breast cancer, as discussed (22,23), planned by other authors (25), or already done retrospectively (10).

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