The effect of metformin on breast cancer outcomes in patients with type 2 diabetes

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Abstract
Observational data suggest that metformin use decreases breast cancer (BC) incidence in women with diabetes; the impact of metformin on BC outcomes in this population is less clear. The purpose of this analysis was to explore whether metformin use influences BC outcomes in women with type 2 diabetes. Prospective institutional databases were reviewed to identify patients with diabetes who received chemotherapy for stages I–III BC from 2000 to 2005. Patients diagnosed with diabetes before or within 6 months of BC diagnosis were included. Males and those with type I, gestational, or steroid-induced diabetes were excluded. Patients were stratified based on metformin use, at baseline, defined as use at time of BC diagnosis or at diabetes diagnosis if within 6 months of BC diagnosis. Kaplan–Meier methods were used to estimate rates of recurrence-free survival (RFS), overall survival (OS), and contralateral breast cancer (CBC). We identified 313 patients with diabetes who received chemotherapy for BC, 141 (45%) fulfilled inclusion criteria and 76 (54%) used metformin at baseline. There were no differences in clinical presentation or tumor characteristics between metformin users and nonusers. At a median follow-up of 87 months (range, 6.9–140.4 months), there was no difference in RFS ($P = 0.61$), OS ($P = 0.462$), or CBC ($P = 0.156$) based on metformin use. Five-year RFS was 90.4% (95% CI, 84–97) in metformin users and 85.4% (95% CI, 78–94) in nonusers. In this cohort of patients with type 2 diabetes receiving systemic chemotherapy for invasive BC, the use of metformin was not associated with improved outcomes.

Introduction
Diabetes mellitus (DM) affects 25.8 million people in the United States; 8.3% of the population [1]. It is estimated that 8–18% of cancer patients have DM [2]. Patients with DM are not only at higher risk for breast cancer (BC) [3, 4] but DM is also believed to worsen BC prognosis [5–8]. Metformin, a biguanide agent, is used as first-line therapy for the treatment of type 2 diabetes, particularly in overweight and obese patients. Emerging laboratory data suggest that this ubiquitous drug has anticancer potential, and observational studies suggest that metformin use decreases overall BC incidence among diabetics [9–12]. While limited, these data have intensified the investigation of metformin and its potential role in BC prevention [13]. At present there are multiple ongoing clinical trials attempting to address the clinical and biological role of metformin in BC.

There are several potential mechanisms by which metformin may impact breast carcinogenesis. In laboratory models, metformin stimulates AMP-activated protein kinase activity, thus inhibiting the mammalian target of rapamycin (mTOR) and decreasing proliferation in BC cell lines [14–16]. Other potentially protective actions of
metformin include inhibition of phosphorylation of IGF-1R/IR [17], inhibition of aromatase expression [18], and reduction in HER2 expression and its tyrosine kinase activity [14, 19]. When used in the management of diabetes, metformin reduces hyperinsulinemia and hyperglycemia, and improves insulin resistance [20], both of which are factors linking diabetes and cancer [21, 22].

Although emerging data would imply the choice of antidiabetic pharmacotherapy might influence the course of BC, the clinical impact remains uncertain. Specifically, whether there is a survival advantage for women newly diagnosed with BC taking metformin is unknown. The study objective was to determine the impact of metformin use on BC outcomes in diabetic women receiving chemotherapy.

Material and Methods

Patients

Prospective institutional databases were retrospectively reviewed to identify patients who reported a diagnosis of DM and received systemic chemotherapy for primary stages I–III BC from 1 January 2000 through 31 December 2005 at Memorial Sloan Kettering Cancer Center (MSKCC). Male patients, those with type 1 DM, gestational, or steroid-induced diabetes, and those diagnosed with DM greater than 6 months after BC diagnosis were excluded. This study was approved by the Institutional Review Board.

Patients were stratified based on metformin use at baseline, defined as use at time of BC diagnosis or at time of diabetes diagnosis if that occurred within 6 months of BC diagnosis. Patient and tumor characteristics, glycemic control agents, cancer treatments, and subsequent BC events were obtained from the medical record and summarized for metformin users and nonusers. Differences were tested using the Wilcoxon rank-sum test for continuous variables and Fisher’s exact test for categorical variables.

Cancer events occurring after diagnosis were classified as local recurrence, regional recurrence, contralateral breast cancer (CBC), or distant metastases. Local recurrence was defined as histologic proven tumor reappearance in the ipsilateral breast or chest wall. Recurrence in the internal mammary, supravacular, or ipsilateral axillary nodes was classified as regional recurrence. All other sites of tumor recurrence were classified as distant metastases. CBCs occurring within 6 months of the index cancer diagnosis were considered synchronous diagnoses; later events were considered CBC.

Time-to-event variables were measured from the date of index surgery, using earliest surgery in cases of bilateral cancer, and censored at the end of follow-up. Recurrence-free survival (RFS) was defined as time until recurrence (local, regional, or distant), or death if the patient died without recurrence. Kaplan–Meier curves were generated for RFS, overall survival (OS), and CBC, stratified on metformin use, and curves were compared using the log-rank test. Women with bilateral cancer at diagnosis and women having contralateral prophylactic mastectomy were not included in the analysis of CBC rates. Cox models were used to assess the effects of stage, age, menopausal status, body mass index (BMI), lymph node positivity, estrogen receptor (ER) status, histologic grade, lymphovascular invasion, and years since diabetes diagnosis on OS and RFS. The effect of metformin on OS and RFS was further assessed in multivariable Cox models after adjusting for age, hormone receptor status, and stage.

Competing risks methods were used to estimate the cumulative incidence of local, regional, and distant recurrence. The first event among local, regional, and distant recurrence and death was counted as the primary event, and any ensuing events were censored at the date of the primary event. Gray’s test was used to compare event rates between the groups in the case of competing risks. All statistical analysis was performed in SAS 9.2 (SAS Institute, Cary, NC) and R 2.11.1 (R Development Core Team, Vienna, Austria), and P-values less than 0.05 were considered significant.

Results

From 2000 to 2005, 2889 patients received chemotherapy for primary stages I–III BC at MSKCC. Of these, 313 (9.2%) patients were documented as having diabetes and 141 (5%) fulfilled study inclusion criteria; 104 patients had type 2 diabetes at BC diagnosis and 37 were diagnosed with DM within 6 months of cancer diagnosis.

Patient demographics and clinical characteristics

Clinical characteristics of the study population are shown in Table 1. The majority of BC patients with DM were postmenopausal 120 (85%) with a median age of 61 years (range, 38–80 years). Median BMI was 32 kg/m² (range, 17–55 kg/m²). There was no difference between metformin users and nonusers with regard to the timing of diabetes diagnosis; 57(92%) of metformin users and 47 (89%) of nonusers were diagnosed with DM prior to their BC diagnosis. The median duration of time for which patients were known to be diabetic prior to BC diagnosis was 5.6 years and 5.3 years in the metformin and no-metformin groups, respectively. Among patients using metformin at baseline, the median duration of metformin use during follow-up, from date of BC diagnosis,
was 5.9 years (range, 30 days–11.7 years). In the no-metformin group, 21 (32.3%) patients managed their diabetes with diet alone. There was no difference in the use of other oral hypoglycemics ($P = 0.496$) or insulin ($P = 0.659$) between the two groups.

Index tumor characteristics are summarized in Table 2. Two women in each group had bilateral BC resulting in the inclusion of 145 tumors in this analysis. There were no differences in clinical stage at diagnosis, final pathologic stage, or any other histologic variables between the two groups. The majority of patients had stage II or III ER-positive invasive ductal cancer. There were no differences in the rate of breast conservation versus mastectomy or adjuvant radiation between metformin users and nonusers. In the small subgroup of patients treated with neoadjuvant chemotherapy ($n = 11$), one patient achieved a complete pathologic response; the patient was in the metformin group.

In a subset analysis of women who had DM prior to their BC diagnosis, we analyzed the presenting features of the cancers in metformin users versus nonusers. There were no differences in histologic subtype (ductal, lobular, other), pathologic stage, nodal status, histologic grade, presence of lymphovascular invasion, or hormone receptor status by metformin use (data not shown).

### Outcomes and survival estimates

At a median follow-up of 87.0 months (range, 6.9–140.4 months), there was no difference in subsequent BC event rates or OS between the two groups (Table 3). Kaplan–Meier curves for RFS (a composite of local, regional, and distant recurrence), OS, and CBC stratified by group (metformin vs. no-metformin) are shown in Figure 1. At 5 years, RFS estimates were 90.4% (95% confidence interval [CI], 83.6–97.2) and 85.4% (95% CI, 76.6–94.3) in metformin users and nonusers, respectively ($P = 0.610$). Five-year OS estimates were 93.0% (95% CI, 87.0–98.9) and 89.7% (95% CI, 81.9–97.5) in metformin users and nonusers, respectively ($P = 0.462$), and CBC rates at 5 years were 3.4% (95% CI, 0–7.9) in the metformin group and 7.9% (95% CI, 0.1–15.1) in the no-metformin group ($P = 0.156$). Although crude rates of all events (local, regional, distant, and CBC) were lower in metformin users; these were not statistically

### Table 1. Study population characteristics.

| Variable                        | No-metformin group ($n = 65$ patients) | Metformin group ($n = 76$ patients) | $P$-value |
|---------------------------------|----------------------------------------|-------------------------------------|-----------|
| Age at BC diagnosis, years      | Median (range) 61 (42–80)              | 59 (38–75)                          | 0.163     |
| Race                            |                                        |                                     | 0.891     |
| Caucasian                       | 31 (47.7%)                             | 41 (54.7%)                          |           |
| African American                | 25 (38.5%)                             | 27 (36.0%)                          |           |
| Asian                           | 6 (9.2%)                               | 4 (5.3%)                            |           |
| Hispanic                        | 2 (3.1%)                               | 2 (2.7%)                            |           |
| Data not available              | 0                                      | 1                                   |           |
| BMI, kg/m²                      | Median (range) 30 (20–55)              | 33 (17–53)                          | 0.316     |
| Postmenopausal                  | 59 (90.8%)                             | 61 (80.3%)                          | 0.099     |
| Prior history of BC             | 5 (7.7%)                               | 3 (3.9%)                            | 0.471     |
| Timing of DM diagnosis          |                                        |                                     | 0.752     |
| Prior to BC diagnosis           | 47 (88.7%)                             | 57 (91.9%)                          |           |
| Within 6 months of BC diagnosis | 6 (11.3%)                              | 5 (8.1%)                            |           |
| Missing                         | 12                                     | 14                                  |           |
| Duration of DM prior to BC, years | Median (range) $3.0$–29.0               | 5.6 (0.4–30.5)                      | 0.979     |
| DM medical management           |                                        |                                     |           |
| Diet control                    | 21 (32.3%)                             |                                     |           |
| Other oral DM medication        | 34 (52.3%)                             | 45 (59.2%)                          | 0.496     |
| Insulin use                     | 13 (20.0%)                             | 12 (15.8%)                          | 0.659     |
| Duration of metformin use, days | Median (range) 2167 (30–4288)          |                                     | NA        |

BC, breast cancer; BMI, body mass index; DM, diabetes mellitus.

1. Among women who were diagnosed with DM prior to BC diagnosis and had date of DM diagnosis available. (Date of DM diagnosis was missing for 26 patients).
2. Other DM therapies included other oral hypoglycemic agents (sulfonylureas and thiazolidinediones).
3. Among women taking metformin at time of BC diagnosis, starting from date of BC diagnosis.
In univariate analysis, disease stage, age, menopausal status, BMI, lymph node positivity, ER status, histologic grade, lymphovascular invasion, and years since diabetes diagnosis were not associated with RFS or OS (all $P > 0.05$, results not shown). In multivariable analysis adjusting for select prognostic variables, metformin use was not associated with improved RFS or OS (Table 4).

### Table 2. Study population: tumor characteristics and treatment.

| Variable                          | No-metformin group ($n = 67$ tumors) | Metformin group ($n = 78$ tumors) | $P$-value |
|-----------------------------------|--------------------------------------|-----------------------------------|-----------|
| Tumor size, cm                    |                                      |                                   |           |
| Median (range)                    | 1.8 (0–6.8)                          | 1.7 (0–6.0)                       | 0.838     |
| Histologic type                   |                                      |                                   | 0.197     |
| Ductal                            | 51 (76.1%)                           | 68 (87.2%)                        |           |
| Lobular                           | 8 (11.9%)                            | 6 (7.7%)                          |           |
| Other                             | 8 (11.9%)                            | 4 (5.1%)                          |           |
| Histologic grade                  |                                      |                                   | 0.178     |
| 1                                 | 3 (5.3%)                             | 0 (0.0%)                          |           |
| 2                                 | 12 (21.1%)                           | 15 (20.8%)                        |           |
| 3                                 | 42 (73.7%)                           | 57 (79.2%)                        |           |
| Lymphovascular invasion           | 26 (40.0%)                           | 32 (41.0%)                        | 1.000     |
| Estrogen receptor                 |                                      |                                   | 0.591     |
| Positive                          | 48 (71.6%)                           | 52 (66.7%)                        |           |
| Negative                          | 19 (28.4%)                           | 26 (33.3%)                        |           |
| Progesterone receptor             |                                      |                                   | 0.240     |
| Positive                          | 33 (49.3%)                           | 30 (38.5%)                        |           |
| Negative                          | 34 (50.7%)                           | 48 (61.5%)                        |           |
| HER2/neu                          |                                      |                                   | 1.000     |
| Positive                          | 11 (16.7%)                           | 13 (16.7%)                        |           |
| Negative                          | 55 (83.3%)                           | 65 (83.3%)                        |           |
| Pathologic stage                  |                                      |                                   | 0.210     |
| I                                 | 19 (28.4%)                           | 14 (18.0%)                        |           |
| II                                | 31 (46.3%)                           | 33 (42.3%)                        |           |
| III                               | 17 (25.4%)                           | 29 (37.2%)                        |           |
| IV                                | 0 (0%)                               | 1 (1.3%)                          |           |
| pCR                               | 0 (0%)                               | 1 (1.3%)                          |           |
| Surgery                           |                                      |                                   | 1.000     |
| Partial mastectomy                | 32 (48.5%)                           | 38 (48.7%)                        |           |
| Mastectomy                        | 34 (51.5%)                           | 40 (51.3%)                        |           |
| Missing                           | 1                                    | 0                                 |           |
| Postmastectomy radiation          | 16/34 (47.1%)                        | 25/40 (62.5%)                     | 0.242     |
| Chemotherapy                      |                                      |                                   | 0.224     |
| Neoadjuvant                       | 3 (4.5%)                             | 8 (10.3%)                         |           |
| Adjuvant                          | 64 (95.5%)                           | 70 (89.7%)                        |           |
| Hormonal therapy (ER/PR+ tumors) | 49 (100.0%)                          | 54 (100.0%)                       | 1.000     |
| Trastuzumab (HER2+ tumors)        | 6 (54.5%)                            | 5 (38.5%)                         | 0.682     |

This cohort was largely treated before the standard use of trastuzumab in the adjuvant setting. pCR, pathologic complete response; ER, estrogen receptor; PR, progesterone receptor.

In multivariable analysis adjusting for select prognostic variables, metformin use was not associated with improved RFS or OS (Table 4).

### Discussion

Metformin is one of the most highly prescribed medications in the United States [23]. In addition to its antidiabetic effects, observational data suggest that metformin may reduce BC risk and potentially alter BC survival. Here we present the results of a single-institution study of women with type 2 DM and invasive BC examining the effect of metformin use on BC outcomes. In this retrospective analysis of 141 women with DM who received chemotherapy for BC, the use of metformin did not result in significant improvements in RFS, OS, or CBC rates at a median follow-up of 7.3 years. It is noteworthy, however, that in this cohort of patients with primarily stage II and III BC requiring chemotherapy in the setting of comorbid disease, the 5-year event rates were considerably lower.
than historical series [24]. This cohort was also largely treated before the standard use of trastuzumab in the adjuvant setting, and 37% of women in our study cohort self-reported as African American, both of which have been associated with poorer BC outcomes [25, 26]. Despite these factors, our 5-year RFS estimates (85.4–90.4%) were better than anticipated.

Prior studies examining the effect of metformin on BC mortality are reviewed in Table 5. The studies from the United Kingdom and China are confounded in that they compare diabetics treated with metformin to nondiabetic patients, making it very difficult to draw conclusions [27, 28], and the other studies generated inconsistent results. Bayraktar et al. [29] analyzed women who received adjuvant chemotherapy for triple-negative BC. After adjustment for age, body weight, tumor size, lymph node status, nuclear grade, lymphovascular invasion, and type of adjuvant chemotherapy received, they found no difference in distant metastasis-free survival, RFS, or OS between 63 diabetic women using metformin and 67 diabetic women not using metformin. In contrast, He et al. [30] found that among diabetic metformin users (n = 88) and nonusers (n = 66) with stage ≥2 HER2+ BC, metformin use was associated with decreased BC-specific mortality (P = 0.023; hazard ratio [HR], 0.47; 95% CI, 0.24–0.90). A recent Canadian population-based study of women ≥66 years of age with diabetes and BC failed to show a significant association between metformin therapy and all-cause mortality (adjusted HR, 0.97; 95% CI, 0.92–1.02) or BC-specific mortality (adjusted HR, 0.91; 95% CI, 0.81–1.03) using a cumulative time-varying exposure approach [31]. However, a direct comparison with previous studies is difficult due to the lack of data on cancer stage and subtype.

It has been proposed that the predominant mechanism of action of metformin may differ across BC molecular subtypes [32], yet at the cellular level, metformin has been shown to inhibit growth in trastuzumab-resistant HER2+ cells [33] and to inhibit cell proliferation and induce apoptosis in triple-negative BC cell lines [34], suggesting that the effect of metformin in the Bayraktar et al. [29] and He et al. [30] studies should have been similar. In our cohort, there were similar proportions of triple-negative cancers among metformin users (22%) and non-users (20%), as well as the same percentage of HER2/neu-positive cancers (16.7%) in each group; however, these numbers were too small for subset analysis.

We did observe a lower rate of CBC in the group using metformin with a Kaplan–Meier estimated 5-year event rate of 7.9 in nonusers and 3.4 in users, suggesting a potential role for metformin in BC prevention, although not statistically significant in our small sample size. Data evaluating the relationship between diabetes and the risk of CBC are limited; however, in a population-based nested case–control study, Li et al. [35] compared 322 women with ER positive BC who developed CBC to 616 matched controls without CBC and demonstrated that diabetics had a 2.2-fold (95% CI, 1.3–3.6) increased risk of CBC. While data regarding the effect of metformin on BC incidence are inconsistent, with several studies showing a risk reduction [9–12] and others showing no benefit [8, 36, 37] or increased risk [38], a recent meta-analysis comparing metformin users to nonusers demonstrated a 6% risk reduction in the incidence of BC in metformin users.

### Table 3. Breast cancer outcomes.

| Follow-up among survivors, months | No-metformin group (n = 65 patients) | Metformin group (n = 76 patients) | P-value |
|----------------------------------|-------------------------------------|----------------------------------|---------|
| Median                           | 88.0                                | 86.4                             | NA      |
| Range                            | 10.6–137.4                          | 6.9–140.4                        |         |
| RFS at 5 years (95% CI)          | 85.4 (76.6–94.3)                    | 90.4 (83.6–97.2)                 | 0.610   |
| OS at 5 years (95% CI)           | 89.7 (81.9–97.5)                    | 93.0 (87.0–98.9)                 | 0.462   |
| CBC rate at 5 years (95% CI)     | 7.9 (0.1–15.1)                      | 3.4 (0–7.9)                      | 0.156   |
| 5-year event rates (95% CI)      |                                    |                                  |         |
| Local                            | 3.1 (0–7.4)                         | 0                                | 0.126   |
| Regional                         | 1.5 (0–4.6)                         | 0                                | 0.917   |
| Distant                          | 9.9 (2.3–17.5)                      | 8.2 (1.9–14.6)                   | 0.876   |
| Number of events                 |                                    |                                  |         |
| OS                               | 12                                  | 10                               |         |
| RFS                              | 13                                  | 13                               |         |
| CBC                              | 5                                   | 2                                |         |
| Local recurrence                 | 2                                   | 0                                |         |
| Regional recurrence              | 1                                   | 1                                |         |
| Distant recurrence               | 7                                   | 9                                |         |

NA, not available; RFS, recurrence-free survival; OS, overall survival; CBC, contralateral breast cancer; CI, confidence interval.

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Therefore, it is plausible that diabetics have a baseline elevated risk of second primary breast malignancy, and if metformin is beneficial in reducing primary breast cancer risk, it may also prove to be beneficial in reducing the risk of CBC.

It is unclear whether metformin influences the development of specific histologic features or alters the clinical presentation of BC, although metformin use among diabetics has been associated with BCs that are less frequently triple negative [40]. Overall, we did not observe a difference in any histopathologic features or hormone receptor status between users and nonusers of metformin.

In the subset of women who had DM prior to their BC diagnosis, there were no differences in histologic subtype, pathologic stage, nodal status, histologic grade, presence of lymphovascular invasion, or hormone receptor status.

Jiralerspong et al. [41] found that diabetic patients with BC treated with metformin experienced higher pathologic response rates after neoadjuvant chemotherapy than those treated with other diabetic medications (24% vs. 8%; \( P = 0.007 \)), although in their study, metformin was not found to be an independent predictor of either RFS or OS after adjusting for diabetic status, age, BMI, stage,
Table 5. Reports of the effect of metformin on breast cancer mortality.

| Study (1st author, country, year) | Design                  | Population                          | Comparison groups                      | N (per group) | Mean age (years) | Median/mean follow-up (years) | Outcome                          | Risk estimates (95% CI) | Adjusting variables                                      |
|----------------------------------|-------------------------|-------------------------------------|----------------------------------------|---------------|-----------------|-----------------------------|----------------------------------|--------------------------|---------------------------------------------------------|
| He X, USA, 2012                  | Retrospective cohort study | Type 2 diabetics with stage ≥2 HER2+ BC | Metformin users vs. nonusers           | 88 vs. 66     | 55              | 4                           | BC-specific mortality            | HR = 0.47 (0.24–0.90), P = 0.023 | Age, BMI, ER/PR status, insulin use                      |
| Bayraktar S, USA, 2012           | Retrospective cohort study | TNBC with DM                        | Non-metformin users vs. metformin users | 67 vs. 63     | 52              | 5.2                         | DMFS Recurrence-free survival   | HR = 1.63 (0.87–3.06), HR = 1.37 (0.78–2.40) | Age, weight, tumor size, LN status, nuclear grade, LVI, type of adjuvant chemotherapy |
| Currie C, UK, 2012               | Retrospective cohort study | BC                                   | Type 2 diabetics vs. nondiabetics      | 1182 vs. 24,393 | —            | 6.8                         | OS                               | HR = 1.32 (1.17–1.49) | Age, smoking, CCI, year of diagnosis, Townsend index of deprivation, number of primary care contacts |
| Hou G, China, 2013               | Retrospective cohort study | BC                                   | Metformin users vs. non-metformin users vs. nondiabetics | 419 vs. 594 vs. 4621 | —            | 5.7                         | OS                               | Metformin vs. no DM HR = 0.76 (0.6–0.97), No metformin vs. no DM HR = 1.71 (1.46–2.0) | Age, TZD, sulfonylurea, insulin use, duration of DM before BC, BC treatments, comorbidity score, DM medication prior to BC |
| Lega I, Canada, 2013             | Population-based cohort study | Women 66 years of age with DM and BC | Metformin users vs. non-metformin users | 1094 vs. 1267 | 77.4          | 4.5                         | All-cause mortality BC-specific mortality | HR = 0.97 (0.92–1.02), HR = 0.91 (0.81–1.03) | Age, TZD, sulfonylurea, insulin use, duration of DM before BC, BC treatments, comorbidity score, DM medication prior to BC |

CI, confidence interval; BC, breast cancer; HR, hazard ratio; BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; DM, diabetes mellitus; DMFS, distant metastasis-free survival; LN, lymph node; LVI, lymphovascular invasion; OS, overall survival; CCI, Charlson Comorbidity index; TZD, thiazolidinediones; TNBC, triple negative breast cancer.
grade, ER/progesterone receptor (PR) status, and neo-
advjuvant taxane use. Among our small subgroup of patients
receiving neoadjuvant chemotherapy (n = 11), there was
one patient who had a complete pathologic response; she
was taking metformin. However, we found no association
between metformin and either RFS or OS.

This study is limited by its retrospective nature and
small sample size. In addition, our cohort consisted pri-
marily of women who self-reported diabetes, with only a
minority being diagnosed by an endocrinologist at our
institution. Additionally, as a cancer center, we did not
have access to patients’ primary care medical records,
which might contain more detailed information on glyce-
mic control, including hemoglobin A1c and insulin levels.
There are also concerns regarding confounding because
metformin-treated patients may have different clinical
characteristics than other diabetes-related treatment
groups, such as those treated with diet alone, which we
may not have been able to detect due to the small sample
size. Yet when we limited our analysis to patients who
developed BC after they were diagnosed with diabetes, we
did not observe any significant differences in clinical pre-
sentation or features of the BCs that developed in metfor-
mintreated patients versus those treated with diet alone
or other agents.

Further research is needed to understand the potential
effects of metformin therapy on BC. Metformin may have
broad activity against carcinogenesis in general, making it
a more attractive chemoprevention agent than disease
site-specific compounds such as tamoxifen or raloxifene
[17]. This may lead to extended therapeutic uses for the
drug. Our failure to show significant beneficial effect of
metformin may represent the true absence of such an ef-
et; or may reflect that our study was underpowered to
detect these effects. Rates of CBC, for example, appeared
to diverge between groups; however, it is likely that a
much larger sample size would be necessary to detect a
difference of the magnitude seen for CBC. In light of
these limitations, we believe our study adds to the accu-
ulating evidence justifying the investigation of the poten-
tial benefits of metformin on BC outcomes and pre-
vention that are underway in many centers in Canada,
Europe, and the United States. These include a large
phase III trial led by the National Cancer Institute of
Canada Clinical Trials Group (MA.32) to evaluate the
effects of metformin in the adjuvant BC setting on sur-
vival outcomes, as well as over 20 clinical trials underway
in the United States investigating metformin’s role in BC.

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Conflict of Interest

None declared.

References

1. National Institute of Diabetes and Digestive and Kidney.
   2011. Diseases: national diabetes statistics fact sheet:
general information and national estimates on diabetes in
the United States. US Department of Health and Human
Services, National Institutes of, Health, Bethesda, MD.
2. Ko, C., and S. Chaudhry. 2002. The need for a
   multidisciplinary approach to cancer care. J. Surg. Res.
   105:53–57.
3. Boyle, P., M. Boniol, A. Koechlin, C. Robertson, F.
   Valenti, K. Coppens, et al. 2012. Diabetes and breast
cancer risk: a meta-analysis. Br. J. Cancer 107:1608–1617.
4. Larsson, S. C., C. S. Mantzoros, and A. Wolk. 2007.
   Diabetes mellitus and risk of breast cancer: a
   meta-analysis. Int. J. Cancer 121:856–862.
5. Kaplan, M. A., Z. Pekkolay, M. Kucukoner, A. Inal, Z.
   Urakci, H. Ertugrul, et al. 2012. Type 2 diabetes mellitus
   and prognosis in early stage breast cancer women. Med.
   Oncol. 29:1576–1580.
6. Chen, W. W., Y. Y. Shao, W. Y. Shau, Z. Z. Lin, Y. S. Lu,
   H. M. Chen, et al. 2012. The impact of diabetes mellitus
   on prognosis of early breast cancer in Asia. Oncologist
   17:485–491.
7. Hou, N., Y. Zheng, E. R. Gamazon, T. O. Ogundiran, C.
   Adebamowo, K. L. Nathanson, et al. 2012. Genetic
   susceptibility to type 2 diabetes and breast cancer risk in
   women of European and African ancestry. Cancer
   Epidemiol. Biomarkers Prev. 21:552–556.
8. Redaniel, M. T., M. Jeffreys, M. T. May, Y. Ben-Shlomo,
   and R. M. Martin. 2012. Associations of type 2 diabetes
   and diabetes treatment with breast cancer risk and
   mortality: a population-based cohort study among British
   women. Cancer Causes Control 23:1785–1795.
9. Bodmer, M., C. Meier, S. Krahenbuhl, S. S. Jick, and C. R.
   Meier. 2010. Long-term metformin use is associated with
decreased risk of breast cancer. Diabetes Care 33:1304–1308.
10. Bosco, J. L., S. Antonsen, H. T. Sorensen, L. Pedersen, and
    T. L. Lash. 2011. Metformin and incident breast cancer
    among diabetic women: a population-based case-control
    study in Denmark. Cancer Epidemiol. Biomarkers Prev.
    20:101–111.
11. Chlebowski, R. T., A. MccTiernan, J. Wactawski-Wende, J.
    E. Manson, A. K. Aragaki, T. Rohan, et al. 2012. Diabetes,
    metformin, and breast cancer in postmenopausal women.
    J. Clin. Oncol. 30:2844–2852.
12. Ruiter, R., L. E. Visser, M. P. van Herk-Sukel, J. W. Coebergh, H. R. Haak, P. H. Geelhood-Duijvestijn, et al. 2012. Lower risk of cancer in patients on metformin in comparison with those on sulfonylurea derivatives: results from a large population-based follow-up study. Diabetes Care 35:119–124.
13. Cuzick, J., A. DeCensi, B. Arun, P. H. Brown, M. Castiglione, B. Dunn, et al. 2011. Preventive therapy for breast cancer: a consensus statement. Lancet Oncol. 12:496–503.
14. Alimova, I. N., B. Liu, Z. Fan, S. M. Edgerton, T. Dillon, S. E. Lind, et al. 2009. Metformin inhibits breast cancer cell growth, colony formation and induces cell cycle arrest in vitro. Cell Cycle 8:909–915.
15. Zakikhani, M., R. Dowling, I. G. Fantus, N. Sonenberg, and M. Pollak. 2006. Metformin is an AMP kinase-dependent growth inhibitor for breast cancer cells. Cancer Res. 66:10269–10273.
16. Dowling, R. J., M. Zakikhani, I. G. Fantus, M. Pollak, and N. Sonenberg. 2007. Metformin inhibits mammalian target of rapamycin-dependent translation initiation in breast cancer cells. Cancer Res. 67:10804–10812.
17. Pollak, M. 2010. Metformin and other biguanides in oncology: advancing the research agenda. Cancer Prev. Res. (Phila.) 3:1060–1065.
18. Brown, K. A., N. I. Hunger, M. Docanto, and E. R. Simpson. 2010. Metformin inhibits aromatase expression in human breast adipose stromal cells via stimulation of AMP-activated protein kinase. Breast Cancer Res. Treat. 123:591–596.
19. Vazquez-Martin, A., C. Oliveras-Ferraros, and J. A. Menendez. 2009. The antidiabetic drug metformin suppresses HER2 (erbB-2) oncoprotein overexpression via inhibition of the mTOR effector p70S6K1 in human breast carcinoma cells. Cell Cycle 8:88–96.
20. Goodwin, P. J., K. I. Pritchard, M. Ennis, M. Clemons, M. Graham, and I. G. Fantus. 2008. Insulin-lowering effects of metformin in women with early breast cancer. Clin. Breast Cancer 8:501–505.
21. Xue, F., and K. B. Michels. 2007. Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. Am. J. Clin. Nutr. 86:823–835.
22. Phoenix, K. N., F. Vumbaca, M. M. Fox, R. Evans, and K. P. Claffey. 2010. Dietary energy availability affects primary and metastatic breast cancer and metformin efficacy. Breast Cancer Res. Treat. 123:333–344.
23. Informatics IIfH. 2012. The use of medicines in the United States: review of 2011.
24. Early Breast Cancer Trialists’ Collaborative G, Peto, R., C. Davies, J. Godwin, R. Gray, H. C. Pan, et al. 2012. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 379:432–444.
25. Newman, L. A., K. A. Griffith, I. Jatoi, M. S. Simon, J. P. Crowe, and G. A. Colditz. 2006. Meta-analysis of survival in African American and white American patients with breast cancer: ethnicity compared with socioeconomic status. J. Clin. Oncol. 24:1342–1349.
26. American Cancer Society. 2011. Breast cancer facts & figures 2011–2012. American Cancer Society, Inc., Atlanta, GA.
27. Hou, G., S. Zhang, X. Zhang, P. Wang, X. Hao, and J. Zhang. 2013. Clinical pathological characteristics and prognostic analysis of 1013 breast cancer patients with diabetes. Breast Cancer Res. Treat. 137:807–816.
28. Currie, C. J., C. D. Poole, S. Jenkins-Jones, E. A. Gale, J. A. Johnson, and C. L. Morgan. 2012. Mortality after incident cancer in people with and without type 2 diabetes: impact of metformin on survival. Diabetes Care 35:299–304.
29. Bayraktar, S., L. F. Hernandez-Aya, X. Lei, F. Meric-Bernstam, J. K. Litton, L. Hsu, et al. 2012. Effect of metformin on survival outcomes in diabetic patients with triple receptor-negative breast cancer. Cancer 118:1202–1211.
30. He, X., F. J. Esteva, J. Ensor, G. N. Hortobagyi, M. H. Lee, and S. C. Yeung. 2012. Metformin and thiazolidinediones are associated with improved breast cancer-specific survival of diabetic women with HER2+ breast cancer. Ann. Oncol. 23:1771–1780.
31. Lega, I. C., P. C. Austin, A. Gruneir, P. J. Goodwin, P. A. Rochon, and L. L. Lipscombe. 2013. Association between metformin therapy and mortality after breast cancer: a population-based study. Diabetes Care 36:3018–3026.
32. Dowling, R. J., S. Niraula, V. Stambolic, and P. J. Goodwin. 2012. Metformin in cancer: translational challenges. J. Mol. Endocrinol. 48:R31–R43.
33. Liu, B., Z. Fan, S. M. Edgerton, X. Yang, S. E. Lind, and A. D. Thor. 2011. Potent anti-proliferative effects of metformin on trastuzumab-resistant breast cancer cells via inhibition of erbB2/IGF-1 receptor interactions. Cell Cycle 10:2959–2966.
34. Liu, B., Z. Fan, S. M. Edgerton, X. S. Deng, I. N. Alimova, S. E. Lind, et al. 2009. Metformin induces unique biological and molecular responses in triple negative breast cancer cells. Cell Cycle 8:2031–2040.
35. Li, C. I., J. R. Daling, M. T. Tang, and K. E. Malone. 2011. Relationship between diabetes and risk of second primary contralateral breast cancer. Breast Cancer Res. Treat. 125:545–551.
36. Currie, C. J., C. D. Poole, and E. A. Gale. 2009. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 52:1766–1777.
37. Libby, G., L. A. Donnelly, P. T. Donnan, D. R. Alessi, A. D. Morris, and J. M. Evans. 2009. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. Diabetes Care 32:1620–1625.
38. Morden, N. E., S. K. Liu, J. Smith, T. A. Mackenzie, J. Skinner, and M. Korc. 2011. Further exploration of the
relationship between insulin glargine and incident cancer: a retrospective cohort study of older Medicare patients. Diabetes Care 34:1965–1971.

39. Zhang, P., H. Li, X. Tan, L. Chen, and S. Wang. 2013. Association of metformin use with cancer incidence and mortality: a meta-analysis. Cancer Epidemiol. 37:207–218.

40. Meiers, P., E. Sharon, W. DongYu, A. Pooni, D. McCready, and W. Leong, eds. 2010. Significant reduction of triple-negative breast cancers in diabetic women on metformin. San Antonio Breast Cancer Symposium, San Antonio, TX.

41. Jiralerspong, S., S. L. Palla, S. H. Giordano, F. Meric-Bernstam, C. Liedtke, C. M. Barnett, et al. 2009. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. J. Clin. Oncol. 27:3297–3302.