Published in final edited form as:

Cancer Causes Control. 2016 May ; 27(5): 709–720. doi:10.1007/s10552-016-0744-3.

Comparative safety of diabetes medications and risk of incident invasive breast cancer: a population-based cohort study

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Abstract

Purpose—Growing evidence suggests that certain commonly used diabetes medications have the potential to differentially alter breast cancer risk. We evaluated the influence of metformin, insulin and sulfonylureas on risk of incident invasive breast cancer.

Methods—We conducted a retrospective cohort study of women ≥40 years of age enrolled in a health plan between 1996 and 2011. Ever, current (<12 months), and duration (<1, 1–2.9, ≥3 years) of diabetes medication use were obtained from pharmacy databases and modeled as time-varying. Multivariable Cox proportional hazards models adjusting for potential confounders including screening mammography and body mass index were used to estimate hazard ratios (HR) and 95% confidence intervals (CI).

Results—Among 10,050 women with diabetes, 57% used metformin, 43% used sulfonylureas, 32% insulin, and 301 were diagnosed with breast cancer over median follow-up of 6.7 years. Results suggested no significant decreased risk of breast cancer among metformin users (HR=0.86;95% CI:0.65–1.12). We found no association between increased breast cancer risk and long-acting insulin (HR=0.95;95% CI:0.51–1.77), but reduced risk with short-/rapid-acting insulin (HR=0.69;95% CI:0.50–0.94), and suggestion of a dose response with increasing duration of short-/rapid-acting insulin use (HR=0.87;95% CI:0.76–1.00). Estimates for sulfonylurea users suggested increased risk with ever use (HR=1.18;95% CI:0.90–1.53) and with longer durations of use (<3 years: HR=1.23;95% CI:0.88–1.73) but confidence intervals included 1.0.

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Compliance with ethical standards

This study was approved by the Group Health institutional review board.

Conflict of Interest

The authors declare that they have no potential conflicts of interest.

Conclusions—Our results provide little support for the previously hypothesized decreased risk of breast cancer with metformin use or for an increased risk with insulin use. Implications for possible residual confounding by screening mammography and comorbidity should be considered in breast cancer pharmacoepidemiology studies.

Keywords

breast cancer; diabetes; metformin; insulin; sulfonylureas; screening mammography

INTRODUCTION

With the increasing prevalence of obesity and an aging population, type 2 diabetes mellitus is rapidly becoming the most common chronic disease in the United States [1]. The association between diabetes and cancer is complex with evidence indicating a 20% increased risk of breast cancer and poorer breast cancer prognosis and mortality among women with diabetes [2-5]. It has been suggested that diabetes medications, such as metformin, might have possible anti-cancer effects. However, the evidence remains inconsistent and sparse.

Lower breast cancer risk among women with diabetes treated with metformin is reported in some, [6-14] but not all, [15-22] epidemiological studies. These and recent meta-analyses [23-27] warrant the ongoing evaluation and consideration of metformin as a viable anti-cancer therapy [28-31]. Risk of breast cancer associated with other diabetic medications is rarely studied and most results are inconclusive. Insulin glargine is associated with increased cancer risk in numerous studies [32-35] but these findings were not consistently confirmed [36], and for insulin analogues other than insulin glargine no increased risk of breast cancer has been reported. While sulfonylureas were reported to have increased risks of colorectal and pancreatic cancers in one study [15], no association was found for breast cancer. Overall, few studies accounted for potentially important confounders including screening mammography [6,18], body mass index (BMI) [14,7,18] and comorbidity [20] in women who were using these medications and those who were not.

To investigate the association between these diabetes agents and incident invasive breast cancer risk among women with diabetes, we conducted a cohort study within a large integrated health system with computerized information on medication use, comorbidity, breast cancer screening, incident breast cancers and risk factors for breast cancer.

MATERIALS AND METHODS

Study Population

We conducted a retrospective cohort study among women enrolled in Group Health Cooperative (GH), a non-profit integrated health system that provides comprehensive health care to approximately 600,000 individuals throughout Washington State and parts of Idaho.

Women aged 40 years and older between January 1, 1996 and December 31, 2011 entered the study cohort at the date of diabetes detection or January 1, 1996, whichever was later. Diabetes was defined as any of the following: (i) pharmacy dispensing for a diabetes

medication; (ii) glycated hemoglobin (HbA1c) $\geq 7.5\%$; (iii) 2+ fasting plasma glucose ≥ 125 mg/dL in a 12-month period; (iv) hospital discharge diagnosis of diabetes (ICD-9 codes 250); or (v) 2+ outpatient diagnoses of diabetes within a 6-month period. Only women enrolled at GH for at least 2 years prior to cohort entry and residing in one of the 13 counties served by the Western Washington Cancer Surveillance System [37], a population-based cancer registry and member of the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute [38], were included in the study. Women were excluded if they had gestational diabetes, breast cancer, or a mastectomy procedure during the 2 years prior to cohort entry. Women were followed until the earliest of breast cancer diagnosis, prophylactic mastectomy, death, disenrollment from GH (defined as a membership lapse of ≥ 92 days) or the end of the study follow-up period (December 31, 2012). The Institutional Review Board at GH approved this study.

Data collection

Data collection spanned from 2 years prior to cohort entry through the end of follow-up.

We used automated health plan pharmacy data to ascertain information on use of metformin, insulin, sulfonylureas and other diabetes medications (e.g., thiazolidinediones) dispensed at GH-owned or contracted pharmacies. We also collected information on pharmacy dispensings of statins, oral contraceptives and hormone replacement therapy (HRT).

We collected potential confounders from GH automated data that contain information on patient demographics, enrollment, inpatient and outpatient diagnoses and procedures including all breast services, laboratory results, pathology, and vital signs. Breast cancer risk factors were obtained through GH's Breast Screening Recruitment and Reminder survey [39] that women complete at the time of each mammography screening and upon turning 40 years of age. Information on deaths was obtained through GH's linkage to the Washington State death tapes [40].

To determine mammography screening, we ascertained exam date and indication designated by the interpreting radiologist from GH administrative databases. We only included screening procedures where the patient reported no symptoms at the time of the exam and the indication was designated as screening [41]. Screening procedures also included all short interval follow-up (SIFU) exams unless the SIFU took place <9 months after a diagnostic exam. A woman was categorized as adherent if she received at least one screening procedure within rolling two year intervals. Less than 1% of screening procedures were breast MRI exams; therefore, we refer to screening procedures as screening mammography.

Exposure Classification

Exposures of interest included metformin, insulin, and sulfonylureas. We did not evaluate diabetes medications other than these classes due to very low prevalence of use. Following the cohort entry date, women were defined as a user of a medication class of interest if they had 2+ dispensings for any medications in the class of interest during any 6-month period that spanned from 2 years prior to cohort entry through end of follow-up. Dispensing data are continuous and thus exposure status was updated daily. Women were allowed to be users of multiple medication classes.

Exposures of interest were further characterized by total duration of use. Duration was estimated by first organizing dispensings into episodes of continuous use. The first episode for a class of interest began with the first dispensing of a medication in that class. For each dispensing, the date when the pills would run out (run-out date) was estimated by multiplying the days' supply by 1.25 to account for an assumed 80% compliance [42]. Successive dispensings with a 60-day gap between the run-out date of one dispensing and date of the subsequent dispensing were considered as continuous use. The end date of a continuous episode was the run-out date of the last dispensing in that episode. Duration was calculated as the amount of time between the start and end dates of the episode. Multiple episodes were summed for total duration of use of each medication class.

Outcomes

Linkage between GH enrollees and the Western Washington SEER tumor registry provided complete ascertainment of breast cancer cases and information on American Joint Committee on Cancer (AJCC) stage [43], histology and hormone receptor status.

Statistical Analysis

We used descriptive statistics to describe patient characteristics by medication exposure and breast cancer status. We used Cox proportional hazards models with time since cohort entry to examine the association between diabetes medication use and risk of incident invasive breast cancer while adjusting for potential confounders. We estimated hazard ratios (HR) and 95% confidence intervals (CI) for metformin, insulin and sulfonylureas all of which were modeled as time-varying exposures. In the analyses of ever vs never use of each of these diabetes medications, women were allowed to transition from being non-users to users as soon as they met the criteria for being a user (i.e., 2 dispensings in 6 months). All three medication classes were included in the same model. In the analyses of current use (defined as any use in prior 12 months), current use of each medication class was evaluated while adjusting for ever use of the other two classes. We also evaluated the relation between duration of diabetes medication use (categorized as 0, <1, 1–2.9, and 3+ years of use) and invasive breast cancer risk among women who had at least 3 years of follow-up. Women entered the duration analyses at 1 year following cohort entry to allow for a 3-year potential exposure period at cohort entry (which included a 2-year exposure period prior to cohort entry). Duration of each diabetes medication class was evaluated while adjusting for ever use of the other two diabetes medication classes in the same model. Linear trend of duration use was also evaluated. For insulin, we further categorized it into any long-acting (LA) insulin use and any short- or rapid (SA/RA)-acting insulin use.

All models were adjusted for variables considered *a priori* to be potential confounders, including: age at cohort entry (40–49 vs 50–59, 60–69, 70–79, 80+ years); study entry year (1996–1999 vs 2000–2003, 2004–2007, 2008–2011); smoking status at entry (current, past vs never/unknown); menopausal status at entry (peri- or premenopausal vs postmenopausal); Charlson comorbidity score [44] (0 vs 1, 2+, time-varying); statin use (ever vs never use, time-varying); HRT (ever vs never use, time-varying); and other diabetes medications (ever vs never use, time-varying). For breast cancer cases, we evaluated tumor characteristics (stage, histology, and hormone receptor status) by medication use and tested differences

using chi-square tests. A statistically significant difference by treatment status was defined as P value ≤ 0.05 .

Because BMI was missing on 46% of women and at least 2 years of follow-up data were required to determine adherence to screening during the study period (missing on 15% of women), adjustment for BMI and mammography screening were done in sensitivity analyses. Among women with available information on BMI, we evaluated diabetes medication use and risk of invasive breast cancer in models with further adjustment for BMI (<25.0 , 25.0 – 29.9 , 30.0 – 34.9 , 35.0 +, time-varying). To adjust for screening mammography, defined as having any screening mammography in past 24 months (time-varying), we restricted the analyses to women who entered the study cohort beginning January 1, 1999 since mammography data was not fully available until 1997. We also explored the proportion of women who were adherent to screening mammography over the first 8 years of study by medication status.

We evaluated the proportional hazards assumption by testing for interaction between the exposures of interest and the logarithm of follow-up time. No evidence suggested violation of the assumptions. All analyses were performed using SAS statistical software version 9.3 (SAS Institute Inc., Cary, North Carolina).

RESULTS

The mean age of the 10,050 women with diabetes was 62 years and the median duration of follow-up was 6.7 years. During the study period, 57% were users of metformin, 32% insulins, 43% sulfonylureas and 1.4% other diabetes agents either alone or in combination (medication use categories not mutually exclusive).

We observed 301 (3%) incident invasive breast cancers during the follow-up. Descriptive statistics on the cohort overall and by breast cancer status are reported in **Table 1**. By individual medication class, incident invasive breast cancers were observed among 2.4% of metformin ever users ($n=135$), 2.0% of insulin ever users ($n=65$) and 3.2% of sulfonylurea ever users ($n=138$) (**Table 1**). Compared to women without breast cancer, cases were older and more likely to be postmenopausal, have more comorbidity per Charlson co-morbidity index of 1+, non-smokers, and have family history of breast cancer. Cases were also more likely to use HRT, less likely to use statins and fewer received mammography screening. For diabetes medications, cases were also less likely to be users of metformin and insulin compared to women without breast cancer. Among women that did not have an incident breast cancer diagnosed during follow up, 13% died ($n=1,239$), 14% disenrolled from GH ($n=1,398$) and 0.2% had a prophylactic mastectomy ($n=19$). Characteristics of women by use of individual diabetes medication classes are reported in **Table 2**.

Among women 52+ years old at cohort entry, adherence to biennial breast screening by use of different diabetes medication classes is described in **Table 3**. At 1 year follow up, adherence to screening mammography was greater among users of metformin (45%) compared to users of insulin (33%) and sulfonylureas (34%). By the third year of follow up, adherence to biennial screening mammography was greater with use of insulin (64%) and

sulfonylureas (65%) than with metformin use (53%). Adherence to screening mammography remained slightly higher in insulin and sulfonylurea users versus metformin throughout the subsequent years of follow up. Adherence in the non-medication group was in the high 50s to low 60s throughout year 1-8 of follow-up.

The majority of breast cancer cases were diagnosed at AJCC stage I (54.8%) or stage II (30.5%). Most tumors were estrogen receptor (ER)-positive (80%), progesterone receptor (PR)-positive (74%) and ductal histology (78%). Fewer tumors of lobular histology were observed among metformin users (6% vs. 16%) vs non-users of metformin (**Table 4**). No differences were observed in breast cancer characteristics by use of insulin or sulfonylureas.

Metformin users had no significantly reduced risk of breast cancer with ever use (HR=0.86; 95% CI, 0.65-1.12) and current use (use in the prior 12 months: HR=0.90; 95% CI, 0.69-1.16) (**Table 4**). A reduced breast cancer risk was observed with 1–2.9 years of metformin use (HR=0.39; 95% CI, 0.19-0.80) vs. non-users, while no apparent association with <1 year and 3+ years of metformin use, and linear trend of duration use was found.

A reduced breast cancer risk was observed among ever users (HR=0.67; 95% CI, 0.50-0.91) and current users (HR=0.64; 95% CI, 0.46-0.88) of insulin (**Table 4**). Analyses of insulin by subtype showed this reduced risk to be specific to SA/RA insulin (HR=0.69; 95% CI, 0.50-0.94). A slight reduced risk of incident breast cancer was also observed with greater duration of insulin use (linear trend, HR=0.86; 95% CI, 0.76-0.98). Estimates for use of sulfonylureas were suggestive of an increased risk with ever use (HR=1.18; 95% CI, 0.90-1.53) and with longer duration of use (3+ years: HR=1.23; 95% CI, 0.88-1.73) but CIs included 1.0.

In sensitivity analyses, risk estimates for metformin use remained similar after adjusting for BMI (N=5,436) and screening mammography (N=6,393). However, adjustment for screening mammography resulted in moving the risk estimates for insulin (HR=0.94; 95% CI, 0.54-1.65) and sulfonylureas (HR=0.96; 95% CI, 0.62-1.48) towards the null. In sensitivity analyses by insulin subtype, risk estimates for SA/RA insulin were no longer statistically significant with adjustment for BMI (HR=0.63; 95% CI, 0.34-1.15) and attenuated toward the null with adjustment for screening mammography (HR=0.87; 95% CI, 0.47-1.59); estimates for LA insulin use increased with adjustment for BMI (HR=1.09; 95% CI, 0.32-3.74) and screening (HR=1.87; 95% CI, 0.69-5.05) but remained non-significant.

DISCUSSION

Results of this study to evaluate commonly used diabetes medications and incident breast cancer risk are in general reassuring. Findings showed no significant association between lower breast cancer risk and use of metformin. SA/RA insulin use was associated with a reduced breast cancer risk but LA insulin and sulfonylureas were not. In fact, our results suggest sulfonylurea users may be at a higher risk for breast cancer. However, further adjustment for breast cancer screening in a subgroup of the cohort raises questions about the robustness of our results and other studies that do not adjust for mammography screening.

The existing literature describing the role of diabetes medications in breast cancer etiology is unclear. For metformin, an inhibitory influence on breast cancer is biologically plausible via AMPK pathways, involvement of tumor suppressor gene LKB1 and inhibition of cell proliferation by mTOR-targeted effects [45,46], but not fully understood. Another recent population-based study from an integrated health system by Soffer, et al. [19] also showed little effect of metformin therapy alone on risk of breast cancer and other gynecological cancers. This study did, however, suggest that the combination of metformin with other diabetes medications lowered the risk of breast cancer compared with metformin alone (HR=0.85, 95% CI 0.69-1.04). This would imply that the potential mechanism by which metformin (and other diabetes medications) affect cancer risk may depend on whether glycemic control was achieved and severity of disease. Many other clinical factors could potentially explain observed associations between diabetes medications and breast cancer screening and risk. Physicians may be less inclined to strongly urge screening mammography in sicker patients taking multiple oral diabetes medications and insulin due to other acute health issues that require immediate attention or limited life expectancy of these patients. In contrast, a patient with well controlled, mild diabetes that is on metformin monotherapy and otherwise healthy may have more opportunity to discuss and receive referrals for screening mammography.

Some preclinical work suggests that metformin influences development of triple negative breast cancers [47], although few epidemiological studies thus far have reported differences based on hormone receptor or HER2-neu status. In one small study of 90 women with breast cancer and diabetes [48], the frequency of PR-positive tumors in women treated with metformin was significantly higher than in women treated with sulfonylureas only ($P=0.043$) or in combination with insulin ($P=0.041$). We found little evidence of differences in hormone receptor status in users of metformin, insulin and sulfonylureas compared to non-users. Further research is needed in this area to elucidate the effects of diabetes medications on breast cancer subtypes.

Our null findings on risk of breast cancer in relation to LA insulin use are consistent with recent meta-analyses [36] that report possibly decreased risk or no association and run counter to others that previously received considerable attention indicating that LA insulin analogues were associated with significantly increased risk of breast cancer. In a large population-based cohort study in the Netherlands [34], users of LA insulin glargine had an increased risk of breast cancer (HR=1.58; 95% CI, 1.22-2.05) compared to users of human insulin. No association was found with non-glargine insulin analogues (HR=0.95; 95% CI 0.83-1.08) in that study [34]. Outside of the hypothesized mitogenic role for insulin analogues in breast cancer [49], studies that observed increased breast cancer risk with LA insulin attributed their findings to confounding by indication. Such a bias could arise if less healthy users or users with more severe diabetes were more likely to develop breast cancer and differentially prescribed LA insulin.

While sulfonylureas were reported to increase risk of colorectal (HR=1.80; 95% CI, 1.29-2.53) and pancreatic cancers (HR=4.95; 95% CI, 2.74-8.96) in one study [15], no association was found with breast cancer (HR=0.98; 95% CI, 0.69-1.41). Similarly, in a nested case-control study in the UK General Practice Research Database [7] neither short-

nor long-term use of sulfonylureas were associated with breast cancer risk. Given the unclear mechanism and slight suggestion of increased risk of breast cancer in our study and other solid tumors in other studies, further investigation of sulfonylureas in relation to cancer risk is warranted.

In several studies, women with diabetes are reported to have lower rates of mammography screening [50-52]. In an analysis of women ages 40-79 years from the Women's Health Initiative clinical trials [6], metformin users had a higher frequency of mammography utilization compared with non-users. In our study, we observed similar patterns of screening in the first year of follow up with greater adherence to biennial mammography among metformin users relative to users of insulin and sulfonylureas. By the third year of follow up, this pattern changed. Adherence to screening mammography was marginally but consistently higher with use of insulin and sulfonylureas than in metformin users. Differences in screening mammography by type of medication use could introduce detection bias to studies of breast cancer risk [53]. The implication of residual confounding in previous studies unable to adjust for breast cancer screening should be considered in light of the change in estimates observed for insulin and sulfonylureas after adjusting for screening.

While our study is the first to provide detailed data on women's screening mammography practices, there are several limitations to be considered. First, our study subjects are from a single health system in Western Washington State and may not be representative of other populations. Further, information on baseline covariates and eligibility criteria for these enrollees only went back two years. While this study included 10,050 women with diabetes (median follow up: 6.7 years), we observed only 301 incident breast cancer cases and some estimates had wide confidence intervals. It is possible that associations between diabetes medications and breast cancer risk would become clearer with greater follow up and/or a larger sample size. Second, we did not have any information about intake of the medications. Thus, patients who fill prescriptions but do not subsequently take the medication may be misclassified as users. Similarly, we only ascertained medication dispensings at pharmacies owned or contracted by However, health plan pharmacy data are considered a robust measure of medication exposure and previous studies find that enrollees obtain 97% of their medications at health plan owned or contracted pharmacies [54,55]. Third, we were only able to perform sensitivity analyses on a subgroup of women to adjust for important covariates such as BMI and screening mammography since these data were not available for all women in the earlier years. The relation between BMI and the diabetes-breast cancer association is complex with the effects of BMI differing by menopausal status and mammography screening [56]. Residual confounding by these covariates and other unknown/unmeasured risk factors is possible. We lacked information on potential confounders such as diet and level of physical activity, and women prescribed and adherent to metformin and other diabetes medications may differ from non-users by factors not measured in this study. Also, not all women in the study had data available on HbA1c at cohort entry and throughout follow up and the possible role of medication adherence and control of diabetes on risk of breast cancer should be evaluated in future studies.

Our study contributes to the growing body of literature on the role of diabetes medications and breast cancer risk and has several key strengths. This population-based cohort of women

enrolled in an integrated health system had longitudinal follow up and complete ascertainment of incident breast cancers based on linkage to the local SEER registry. We had comprehensive data on medication use based on pharmacy dispensing that allowed us to model breast cancer risk in relation to duration and time-varying use of diabetes medications. We adjusted for many important confounders including BMI and mammography screening. We were also able to report on tumor characteristics and mammography screening adherence by diabetes medication use.

Our study indicates no association between use of long-acting insulin and breast cancer risk, and short-/rapid-acting insulin use may possibly reduce breast cancer risk. We demonstrated little evidence to suggest that metformin use reduces breast cancer risk among women with diabetes. However, the chemopreventive effects of metformin remain to be fully understood and questions regarding a possible role for metformin in adjuvant breast cancer therapy will be better answered from ongoing clinical trials [31].

Acknowledgments

This study was supported by the U.S. National Institutes of Health (grant number R03CA167589 to D.M.B.) at Group Health Research Institute.

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Table 1

Descriptive characteristics of women with diabetes by breast cancer outcome

	All women (N=10,050)		Non-cases (n=9,749)		Breast cancer cases (n=301)	
	n	(%)	n	(%)	n	(%)
<i>Characteristics at study entry</i>						
Age, years						
Mean (SD)	61.6	(12.3)	61.5	(12.3)	63.4	(10.7)
40 – 49	1,831	(18.2)	1,798	(18.4)	33	(11.0)
50 – 59	2,964	(29.5)	2,882	(29.6)	82	(27.2)
60 – 69	2,480	(24.7)	2,388	(24.5)	92	(30.6)
70 – 79	1,869	(18.6)	1,792	(18.4)	77	(25.6)
80+	906	(9.0)	889	(9.1)	17	(5.6)
Year of study entry						
1996 – 1999	4,025	(40.0)	3,842	(39.4)	183	(60.8)
2000 – 2003	1,569	(15.6)	1,525	(15.6)	44	(14.6)
2004 – 2007	2,183	(21.7)	2,131	(21.9)	52	(17.3)
2008 – 2011	2,273	(22.6)	2,251	(23.1)	22	(7.3)
Menopausal status						
Peri- or Premenopausal	2,926	(29.1)	2,865	(29.4)	61	(20.3)
Postmenopausal	7,124	(70.9)	6,884	(70.6)	240	(79.7)
Race						
White	7,491	(81.7)	7,239	(81.7)	252	(84)
African American	570	(6.2)	556	(6.3)	14	(4.7)
American Indian/Alaska Native	221	(2.4)	215	(2.4)	6	(2.0)
Asian/Pacific Islander	883	(9.6)	855	(9.6)	28	(9.3)
Unknown	885		884		1	
Ethnicity						
Not Hispanic	8,859	(94.9)	8,579	(94.9)	280	(93.3)
Hispanic	480	(5.1)	460	(5.1)	20	(6.7)
Unknown	711		710		1	
Education						
High school or less	1,482	(30.4)	1,437	(30.4)	45	(31.0)
Some college	1,944	(39.9)	1,888	(39.9)	56	(38.6)
College or post graduate	1,450	(29.7)	1,406	(29.7)	44	(30.3)
Unknown	5,174		5,018		156	
Body mass index (kg/m²)						
Mean (SD)	33.9	(8.3)	33.9	(8.3)	32.9	(7.0)
< 25.0	697	(12.8)	684	(12.9)	13	(10.0)
25.0 – 29.9	1,247	(22.9)	1,211	(22.8)	36	(27.7)
30.0 – 34.9	1,356	(24.9)	1,323	(24.9)	33	(25.4)
35.0+	2,136	(39.3)	2,088	(39.4)	48	(36.9)
Unknown	4,614		4,443		171	

	All women (N=10,050)		Non-cases (n=9,749)		Breast cancer cases (n=301)	
	n	(%)	n	(%)	n	(%)
Smoking status						
Current	552	(5.5)	544	(5.6)	8	(2.7)
Past	1,195	(11.9)	1,175	(12.1)	20	(6.6)
Never/Unknown	8,303	(82.6)	8,030	(82.4)	273	(90.7)
Family history of breast cancer (1st degree)						
No	3,149	(78.2)	3,069	(78.6)	80	(67.2)
Yes	877	(21.8)	838	(21.4)	39	(32.8)
Unknown	6,024		5,842		182	
Charlson score						
0	4,362	(43.4)	4,254	(43.6)	108	(35.9)
1	4,096	(40.8)	3,944	(40.5)	152	(50.5)
2+	1,592	(15.8)	1,551	(15.9)	41	(13.6)
Glycated hemoglobin (HbA1c) [‡]						
Mean (SD)	7.8	(2.1)	7.8	(2.1)	7.9	(2.0)
7%	2,454	(48.1)	2,393	(48.2)	61	(44.5)
>7%	2,648	(51.9)	2,572	(51.8)	76	(55.5)
Unknown	4,948		4,784		164	
Characteristics through end of follow-up for breast cancer						
Median years of follow-up (IQR)	6.7	(3.2–12.7)	6.8	(3.3–12.8)	5.3	(2.0–10.0)
Other medication use						
Hormone replacement therapy	3,076	(30.6)	2,965	(30.4)	111	(36.9)
Oral contraceptives	276	(2.7)	273	(2.8)	3	(1.0)
Statins	7,300	(72.6)	7,114	(73.0)	186	(61.8)
Diabetes medication use						
Metformin	5,700	(56.7)	5,565	(57.1)	135	(44.9)
Sulfonylurea	4,319	(43.0)	4,181	(42.9)	138	(45.8)
Insulin [§]	3,226	(32.1)	3,161	(32.4)	65	(21.6)
Long-acting insulin	770	(23.9)	758	(24.0)	12	(18.5)
Short-acting insulin	3,014	(93.4)	2,949	(93.3)	65	(100)
Rapid-acting insulin	1,145	(35.5)	1,128	(35.7)	17	(26.2)
Short- or rapid-acting insulin	3,163	(98.0)	3,098	(98.0)	65	(100)
Other diabetes medications [*]	142	(1.4)	138	(1.4)	4	(1.3)

[‡]Most recent HbA1c prior to cohort entry

[‡]Column % excluding women with <2 years of follow up

[§]Type of insulin use not mutually exclusive

^{*}Other diabetes medications: thiazolidinediones, alpha-glucosidase inhibitors, DPP-4 inhibitors, meglitinides, exenatide, and pramlintide

Table 2
Descriptive characteristics of women with diabetes by ever/never use of diabetes medication classes

	Metformin				Insulin				Sulfonylureas			
	Users (n=5,700)	Non-users (n=4,350)	n (%)		Users (n=3,226)	Non-users (n=6,824)	n (%)		Users (n=4,319)	Non-users (n=5,731)	n (%)	
<i>Characteristics at study entry</i>												
Age, years												
Mean (SD)	57.3 (10.0)	67.1 (12.7)			59.7 (12.1)	62.5 (12.2)			60.7 (12.3)	62.2 (12.2)		
40 – 49	1,359 (23.8)	472 (10.9)			764 (23.7)	1,067 (15.6)			942 (21.8)	889 (15.5)		
50 – 59	2,184 (38.3)	780 (17.9)			972 (30.1)	1,992 (29.2)			1,249 (28.9)	1,715 (29.9)		
60 – 69	1,408 (24.7)	1,072 (24.6)			728 (22.6)	1,752 (25.7)			1,003 (23.2)	1,477 (25.8)		
70 – 79	642 (11.3)	1,227 (28.2)			552 (17.1)	1,317 (19.3)			789 (18.3)	1,080 (18.8)		
80+	107 (1.9)	799 (18.4)			210 (6.5)	696 (10.2)			336 (7.8)	570 (9.9)		
Year of study entry												
1996 – 1999	2,172 (38.1)	1,853 (42.6)			2,090 (64.8)	1,935 (28.4)			2,546 (58.9)	1,479 (25.8)		
2000 – 2003	972 (17.1)	597 (13.7)			516 (16.0)	1,053 (15.4)			766 (17.7)	803 (14.0)		
2004 – 2007	1,306 (22.9)	877 (20.2)			388 (12.0)	1,795 (26.3)			654 (15.1)	1,529 (26.7)		
2008 – 2011	1,250 (21.9)	1,023 (23.5)			232 (7.2)	2,041 (29.9)			353 (8.2)	1,920 (33.5)		
Menopausal status												
Peri- or Premenopausal	2,189 (38.4)	737 (16.9)			1,164 (36.1)	1,762 (25.8)			1,412 (32.7)	1,514 (26.4)		
Postmenopausal	3,511 (61.6)	3,613 (83.1)			2,062 (63.9)	5,062 (74.2)			2,907 (67.3)	4,217 (73.6)		
Race												
White	4,185 (80.2)	3,306 (83.7)			2,575 (83.9)	4,916 (80.6)			3,276 (81.6)	4,215 (81.9)		
African American	321 (6.2)	249 (6.3)			211 (6.9)	359 (5.9)			274 (6.8)	296 (5.7)		
American Indian/Alaska Native	156 (3.0)	65 (1.6)			77 (2.5)	144 (2.4)			101 (2.5)	120 (2.3)		
Asian/Pacific Islander	555 (10.6)	328 (8.3)			205 (6.7)	678 (11.1)			366 (9.1)	517 (10.0)		
Unknown	483	402			158	727			302	583		
Ethnicity												
Not Hispanic	4,969 (94)	3,890 (96)			2,969 (95.2)	5,890 (94.7)			3,863 (94.3)	4,996 (95.3)		
Hispanic	319 (6.0)	161 (4.0)			151 (4.8)	329 (5.3)			232 (5.7)	248 (4.7)		
Unknown	412	299			106	605			224	487		

	Metformin				Insulin				Sulfonylureas			
	Users (n=5,700)	n	(%)	Non-users (n=4,350)	Users (n=3,226)	n	(%)	Non-users (n=6,824)	Users (n=4,319)	n	(%)	Non-users (n=5,731)
Education												
High school or less	766	(26.8)	716	(35.4)	359	(29.0)	1,123	(30.9)	622	(34.3)	860	(28.1)
Some college	1,218	(42.7)	726	(35.9)	548	(44.2)	1,396	(38.4)	756	(41.7)	1,188	(38.8)
College or post graduate	870	(30.5)	580	(28.7)	332	(26.8)	1,118	(30.7)	435	(24.0)	1,015	(33.1)
Unknown	2,846		2,328		1,987		3,187		2,506		2,668	
Body mass index (kg/m²)												
Mean (SD)	35.7	(8.1)	31.5	(7.9)	33.9	(8.3)	33.9	(8.3)	34.3	(8.2)	33.7	(8.3)
< 25.0	212	(6.8)	485	(20.0)	160	(13.2)	537	(12.7)	195	(11.0)	502	(13.6)
25.0 – 29.9	597	(19.2)	650	(28)	264	(21.9)	983	(23.2)	406	(23.0)	841	(22.9)
30.0 – 34.9	804	(25.8)	552	(23.8)	308	(25.5)	1,048	(24.8)	446	(25.3)	910	(24.8)
35.0+	1,503	(48.2)	633	(27.3)	476	(39.4)	1,660	(39.3)	718	(40.7)	1,418	(38.6)
Unknown	2,584		2,030		2,018		2,596		2,554		2,060	
Smoking status												
Current	371	(6.5)	181	(4.2)	141	(4.4)	411	(6.0)	199	(4.6)	353	(6.2)
Past	669	(11.7)	526	(12.1)	187	(5.8)	1,008	(14.8)	300	(6.9)	895	(15.6)
Never/Unknown	4,660	(81.8)	3,643	(83.7)	2,898	(89.8)	5,405	(79.2)	3,820	(88.4)	4,483	(78.2)
Family history of breast cancer (1st degree)												
No	1,844	(79.5)	1,305	(76.5)	813	(76.7)	2,336	(78.8)	1,194	(79.4)	1,955	(77.5)
Yes	476	(20.5)	401	(23.5)	247	(23.3)	630	(21.2)	310	(20.6)	567	(22.5)
Unknown	3,380		2,644		2,166		3,858		2,815		3,209	
Charlson score												
0	2,852	(50.0)	1,510	(34.7)	1,181	(36.6)	3,181	(46.6)	1,776	(41.1)	2,586	(45.1)
1	2,316	(40.6)	1,780	(40.9)	1,466	(45.4)	2,630	(38.5)	1,919	(44.4)	2,177	(38.0)
2+	532	(9.3)	1,060	(24.4)	579	(17.9)	1,013	(14.8)	624	(14.4)	968	(16.9)
Glycated hemoglobin (HbA1c) [‡]												
Mean (SD)	8.3	(2.2)	7.0	(1.5)	8.8	(2.5)	7.5	(1.8)	8.6	(2.3)	7.3	(1.7)
7%	1,109	(34.8)	1,345	(70.3)	312	(27.3)	2,142	(54.1)	550	(28.3)	1,904	(60.2)
>7%	2,081	(65.2)	567	(29.7)	831	(72.7)	1,817	(45.9)	1,391	(71.7)	1,257	(39.8)

	Metformin		Insulin		Sulfonylureas	
	Users (n=5,700)	Non-users (n=4,350)	Users (n=3,226)	Non-users (n=6,824)	Users (n=4,319)	Non-users (n=5,731)
Unknown	2,510	2,438	2,083	2,865	2,378	2,570
<i>Characteristics through end of follow-up for breast cancer</i>						
Median years of follow-up (IQR)	8.4 (4.5-14)	4.8 (2.2-9.6)	11.9 (5.6-17)	5.5 (2.7-9.5)	10.5 (5.1-16)	5.1 (2.5-8.8)
Other medication use						
Other diabetes medications [*]	131 (2.3)	11.0 (0.3)	98 (3.0)	44 (0.6)	105 (2.4)	37 (0.6)
Hormone replacement therapy	1,912 (33.5)	1,164 (26.8)	1,285 (39.8)	1,791 (26.2)	1,619 (37.5)	1,457 (25.4)
Oral contraceptives	196 (3.4)	80.0 (1.8)	102 (3.2)	174 (2.5)	114 (2.6)	162 (2.8)
Statins	4,904 (86)	2,396 (55.1)	2,555 (79.2)	4,745 (69.5)	3,466 (80.3)	3,834 (66.9)

[‡] Most recent HbA1c prior to cohort entry

^{*} Other diabetes medications: thiazolidinediones, alpha-glucosidase inhibitors, DPP-4 inhibitors, meglitinides, exenatide, and pramlintide

[†] Column % excluding women with <2 years of follow up

Table 3Screening mammography during years of study follow up by diabetes medication use[‡]

	All women [†]	Metformin users	Insulin users	Sulfonylurea users	Diabetes medication non-users
Year	% Adherent to biennial screening mammography [§]				
0	40	32	9	9	51
1	53	45	33	34	59
2	61	55	55	59	62
3	62	53	64	65	62
4	62	57	68	67	61
5	60	55	67	66	60
6	60	58	69	68	59
7	62	60	70	67	61
8	60	59	66	64	59

[‡] Among women 52+ years old at cohort entry; medication use categories not mutually exclusive[†] All women (N=7,650); metformin users (n=870); insulin users (n=682); sulfonylurea users (n=1,200); diabetes medication non-users (n=5,300) at cohort entry year. Other diabetes medication users were not included due to small numbers.[§] Women with a screening mammogram in 24 months prior to cohort entry (Year 0) and 27 months prior to each follow up year (Years 1-8)

Descriptive characteristics of breast cancer cases by ever/never use of diabetes medication classes in 2 years prior to cohort entry through end of study follow up

Table 4

	Metformin			Insulin			Sulfonylureas		
	Users (n=115)	Non-users (n=186)	P value [‡]	Users (n=65)	Non-users (n=236)	P value [‡]	Users (n=138)	Non-users (n=163)	P value [‡]
AJCC stage	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
I	75 (55.6)	90 (54.2)	0.491	36 (55.4)	129 (54.7)	0.171	75 (54.3)	90 (55.2)	0.783
II	42 (31.1)	50 (30.1)		14 (21.5)	78 (33.1)		40 (29.0)	52 (31.9)	
IIIA	8 (5.9)	8 (4.8)		5 (7.7)	11 (4.7)		8 (5.8)	8 (4.9)	
IIIB – IV	8 (5.9)	9 (5.4)		6 (9.2)	11 (4.7)		8 (5.8)	9 (5.5)	
Unknown	2	9		4	7		7	4	
Histology									
Lobular	7 (6.1)	29 (15.6)	0.046	4 (6.2)	32 (13.6)	0.245	13 (9.4)	23 (14.1)	0.378
Ductal	96 (83.5)	138 (74.2)		53 (81.5)	181 (76.7)		112 (81.2)	122 (74.8)	
Mixed	12 (10.4)	19 (10.2)		8 (12.3)	23 (9.7)		13 (9.4)	18 (11.0)	
Hormone receptor status									
ER– / PR–	15 (13.0)	24 (12.9)	0.456	11 (16.9)	28 (11.9)	0.311	22 (15.9)	17 (10.4)	0.558
ER+ / PR–	5 (4.3)	5 (9.7)		2 (3.1)	21 (8.9)		8 (5.8)	15 (9.2)	
ER– / PR+	2 (1.7)	2 (1.6)		0 (0)	5 (2.1)		2 (1.4)	3 (1.8)	
ER+ / PR+	85 (73.9)	85 (71.5)		48 (73.8)	170 (72.0)		99 (71.7)	119 (73.0)	
ER and PR unknown	8	8		4	12		7	9	

[‡] χ^2 tests for categorical variables (or Fisher's exact test with cells <5) were used to test for differences between groups

Table 5

Risk of invasive breast cancer in relation to diabetes medication use

	Metformin			Insulin			Short-/rapid-acting insulin			Sulfonylureas		
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
<i>Ever versus never use</i>												
Never		Reference		Reference		Reference		Reference		Reference		Reference
Ever	0.86	(0.65-1.12)	0.67	(0.50-0.91)	0.95	(0.51-1.77)	0.69	(0.50-0.94)	1.18	(0.90-1.53)		
Never/past use		Reference		Reference		Reference		Reference		Reference		
Current use	0.90	(0.69-1.16)	0.64	(0.46-0.88)	1.04	(0.53-2.03)	0.66	(0.47-0.92)	0.88	(0.67-1.15)		
<i>Duration</i>												
Never		Reference		Reference		Reference		Reference		Reference		
<1 year	0.92	(0.52-1.61)	0.80	(0.49-1.30)	0.93	(0.34-2.55)	0.79	(0.49-1.30)	1.21	(0.80-1.84)		
1 – 2.9 years	0.39	(0.19-0.80)	0.62	(0.34-1.13)	0.80	(0.25-2.56)	0.68	(0.38-1.22)	1.15	(0.76-1.74)		
3+ years	1.14	(0.68-1.91)	0.68	(0.45-1.01)	1.08	(0.43-2.73)	0.69	(0.45-1.06)	1.23	(0.88-1.73)		
Linear trend of duration	0.95	(0.80-1.13)	0.86	(0.76-0.98)	0.99	(0.75-1.31)	0.87	(0.76-1.00)	1.07	(0.96-1.19)		

Abbreviations: HR, hazard ratio; CI, confidence interval

Note: Hazard ratios and 95% CIs for diabetes medications classes of interest (metformin, insulin, and sulfonylureas) were estimated from multivariable models adjusting for other diabetes medications, age at cohort entry, study entry year, smoking status, menopausal status, Charlson score, statin use, and menopausal hormone therapy.