Research Article

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Metformin and Incident Breast Cancer among Diabetic Women: A Population-Based Case–Control Study in Denmark

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Abstract

Background: Preliminary evidence suggests that metformin may decrease breast cancer risk by decreasing insulin levels and reducing cell proliferation. We evaluated the effect of metformin medication on the risk of incident breast cancer among peri- and postmenopausal women.

Methods: We used Danish medical registries to conduct a nested case–control study among type 2 diabetic women 50 years or older who resided in northern Denmark from 1989 to 2008 ($n = 4,323$). We identified 393 diabetic cases and used risk-set sampling to select 10 diabetic controls per case ($n = 3,930$) matched on county of residence. Odds ratios (OR) and 95% CIs were estimated by conditional logistic regression associating metformin use with breast cancer occurrence.

Results: Ninety-six cases (24%) and 1,154 controls (29%) used metformin for at least 1-year duration. Cases were slightly older on average than controls, but they were similar in distribution for parity, use of hormone replacement therapy, and history of diabetes complications. Metformin users were less likely with a diagnosis of breast cancer (OR = 0.77; 95% CI = 0.61–0.99) than nonmetformin users. Adjustment for diabetes complications, clinically diagnosed obesity, and important predictors of breast cancer did not substantially alter the association (OR = 0.81; 95% CI = 0.63–0.96).

Conclusion: Our results suggest that metformin may protect against breast cancer in type 2 diabetic peri- or postmenopausal women.

Impact: This study supports the growing evidence of a role for metformin in breast cancer chemoprevention. *Cancer Epidemiol Biomarkers Prev; 20(1); 101–11. ©2011 AACR.*

Introduction

Insulin increases proliferation and decreases apoptosis of cells (1, 2). Type 2 diabetic patients have higher levels of circulating insulin (3–6) and have an increased risk of incident breast cancer compared with nondiabetic women (3). Untransformed at-risk breast epithelial cells have insulin receptors, which suggests that insulin modulation may affect breast cancer risk (7).

Metformin is a well-tolerated biguanide medication (8) used to decrease circulating insulin levels among diabetic patients (9). It acts on hepatocytes to reduce glucose output and may also operate in at-risk epithelial cells to directly reduce protein synthesis and proliferation. As a secondary consequence, metformin lowers elevated insulin levels among diabetic patients (9). Metformin indirectly reduces the level of circulating insulin in diabetic patients and may reduce the rate of cell proliferation in epithelial cells; therefore, it may also reduce the risk of breast cancer (9). In a bioassay of mice, adenocarcinomas occurred 4 times more frequently among untreated mice than among mice treated with phenformin, a biguanide similar to metformin that was withdrawn from clinical use in the 1970s because of side effects (10).

Three observational studies have evaluated the effect of metformin on breast cancer risk (5, 11, 12). Two European cohort studies evaluated all cancer risk as their primary outcome and then subsequently evaluated breast cancer risk. The first study observed that Scottish women with a first prescription of metformin ($N = 3,723$) had a 40% lower incidence of breast cancer than those who had no record of metformin prescription, but only 24 breast cancer cases were exposed to metformin (11). A second study was conducted in The Health Information Network, a subset of the United Kingdom General Practice

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Database, ($N = 27,654$), and did not observe any substantial association between any antidiabetic treatment—sulfonylureas, sulfonylureas plus metformin, insulin (Hazard Ratio = 0.90, 0.98, and 1.07, respectively)—and incident breast cancer risk compared with metformin only users (5). Potential confounding by predictors of breast cancer, such as menopausal status, parity, and age at first birth, was uncontrolled. A recent case–control study using the UK General Practice Database ($N = 1,458$) reported no overall association between any metformin use and breast cancer risk but observed a 56% decreased risk of breast cancer associated with long-term metformin use (~5-year duration) compared with other antidiabetic medication use. However, this inverse association was based on only 17 exposed breast cancer cases (12). None of these 3 studies restricted or stratified by menopausal status, an important modifier to consider because the effect of breast cancer risk factors often varies by menopausal status.

These limitations, and others described later, were taken into account in the design of this study so as to improve the validity of the available evidence. The objective of the present study was to evaluate the effect of metformin medication on the risk of incident breast cancer among peri- and postmenopausal type 2 diabetic women. We hypothesized that diabetic women who used metformin would have a lower risk of breast cancer than diabetic women who did not use metformin.

Materials and Methods

Study population

We conducted this population-based case–control study among diabetic patients in northern Denmark nested within a source population identified from the Danish National Registry of Patients covering Danish hospitals (13). The Danish National Health Service provides universal tax-supported health care, including unfettered access to primary and hospital care, and reimbursement for most prescription medications (13). Since 1968, all Danish residents have been assigned a unique civil personal registration (CPR) number that encodes sex and date of birth (13). The CPR number is used in all medical registries, allowing direct linkage among them. All nonpsychiatric inpatient hospital admissions have been recorded in the Danish National Registry of Patients since 1977. Beginning in 1995, outpatient hospital visits and emergency department visits were also recorded. Our source population consisted of female residents of Aarhus, North Jutland, Viborg, and Ringkøbing counties in northern Denmark (1.8 million) during the calendar periods when their respective county prescription registries were available. The North Jutland prescription database began in 1989, Aarhus in 1996, and Ringkøbing and Viborg in 1998 (14). The nationwide prescription registry did not start until 1995. Therefore, we used the county-specific prescription databases to capture prescriptions closer to when metformin was introduced as a treatment of diabetes in Denmark, at least in North Jutland.

Antidiabetic medications are available only by prescription in Denmark and are dispensed at pharmacies equipped with automated electronic reporting systems (14). The prescription databases track all filled prescriptions for reimbursed drugs dispensed by all pharmacies in the 4 counties (14). These databases encode drugs according to the Anatomical Therapeutic Chemical (ATC) classification system (15) and record dates for redemption of all prescriptions, type, and quantity of medication (product number, product amount, and package size), along with each patient's unique CPR number (14).

We restricted the population to women with type 2 diabetes, identified by an outpatient or inpatient discharge diagnosis of type 2 diabetes. We excluded diabetic patients who did not live in any of the 4 counties for at least 2 years after their diabetes diagnosis to ensure that sufficient prescription data would be available. We also excluded women with a cancer diagnosis preceding their diabetes diagnosis (except nonmelanoma skin cancer). This study was approved by the Danish Registry Board (approval no. 2004-41-4693).

Analytic variables

We identified incident breast cancer cases in the source population by linking to the Danish Cancer Registry using ICD (International Classification of Disease)-8 codes or ICD-10 codes for breast cancer. The Danish Cancer Registry has recorded all incident cancers through December 31, 2008 (16), and has near 100% completeness for breast cancer diagnosis (17). We excluded women diagnosed with *in situ* breast cancer from the case subjects ($N = 132$). We selected control subjects by sampling the risk-set of women who were members of the source population (18), residents in the same county, and without a diagnosis on the date of the case's breast cancer diagnosis. We selected 10 controls at random from the set of matched controls when more than 10 were eligible and included all eligible controls when the risk-set of matched controls included 10 or fewer. The index date for case subjects was the date of breast cancer diagnosis. The index date for diabetic control subjects was the date of breast cancer diagnosis for their matched diabetic case. Inferred menopausal status was based on age (premenopausal <50 years at index date; peri-/postmenopausal $\geq$50 years at index date). After an initial analysis, we further restricted the source population to peri-/postmenopausal women ($N = 4,323$) because only 3 premenopausal breast cancer cases used metformin before their breast cancer diagnosis.

In Denmark, all diabetic patients are treated with a diet and exercise regimen. If the regimen is inadequate to control diabetes, patients are prescribed antidiabetic medications (19). We assessed treatment for type 2 diabetes by oral or injectable antidiabetic medications by linking the case and control subjects to the prescription registry by the CPR number. Prescriptions were

identified using the ATC code for insulin (ATC prefix A10A) and oral antidiabetic medications (ATC prefix A10B). Metformin users included women who redeemed prescriptions for metformin for a minimum of 1-year duration between January 1, 1989, and December 31, 2008, and before their index date. We calculated duration of use by multiplying the number of prescriptions by amount of pills per prescription and limiting to the total accumulated before the index date. Former users were defined as women whose last metformin prescription was greater than 1 year before the index date. Women whose last metformin prescription was within 1 year of the index date were considered recent users. The nonmetformin reference group consisted of women who used other oral or injectable antidiabetic medications for a minimum of 1-year duration preceding the index date ($n = 2,197$) and women who did not receive medication (diet and exercise only) to treat their diabetes ($n = 876$). Women who did not receive any antidiabetic medication, plus women who switched medications or had less than 1 year of metformin use during the entire observation period ($n = 472$) but were prescribed other antidiabetic medications for a year or longer, were also classified in the reference group.

On the basis of literature review of established risk factors for breast cancer, we considered the following variables *a priori* to be candidate confounders: age at index date, postmenopausal hormone replacement therapy use, parity, preceding diagnosis of polycystic ovarian syndrome (PCOS), complications due to diabetes before the index date, and clinically diagnosed obesity. We used complications due to diabetes as a proxy for severity of diabetes, and we identified complications from an algorithm using the ICD codes recorded in the Danish National Registry of Patients. Diabetes complications included eye damage, kidney damage, peripheral nerve damage, myocardial infarction, stroke, or peripheral artery disease diagnosed at or after the diabetes diagnosis but before the index date. Because weight and height are not routinely collected in the registries, we used clinically diagnosed obesity as a surrogate for obesity measured by body mass index. We identified clinically diagnosed obesity before the index date using the ICD-10 classification system, as weight and height could not be obtained from the registries. We derived age at index date (years) from subjects' CPR number and parity by linking with their offspring's CPR numbers. We used the prescription database to ascertain postmenopausal hormone replacement therapy use. History of PCOS was ascertained from the Danish National Registry of Patients using ICD codes because PCOS has been associated with breast cancer occurrence in some studies (20), and metformin is the indicated treatment option for PCOS patients (21). All ICD-8 and ICD-10 codes used to identify breast cancer, type 2 diabetes, diabetes complications, clinical obesity, and PCOS can be found in Appendix A. All ATC codes used to identify hormone replacement therapy and antidiabetic medications can be found in Appendix B.

Statistical analysis

We used contingency table analysis to describe the population of type 2 diabetic women. Family CPR numbers could not be used to infer parity reliably for the oldest women (22), so we used Markov chain multiple imputation methods to impute parity when it was missing (23).

We used conditional logistic regression to control for matching on county of residence. We calculated odds ratios (OR) and 95% CIs to estimate the association between incident breast cancer and metformin use. Given the risk-set sampling design, the ORs provide unbiased estimates of the corresponding incidence rate ratios (18). We adjusted for diabetes complications and clinical obesity and then further adjusted for age at index date, year of birth, parity, and use of postmenopausal hormone replacement therapy. We evaluated duration of metformin use as a continuous variable as well as a categorical variable. In addition, we assessed whether severity of diabetes modified the association between metformin use and breast cancer risk by stratifying by diabetes complications. We estimated the effect of metformin monotherapy, defined as using only metformin to treat diabetes before the index date, on the risk of breast cancer relative to nonmetformin users. We repeated the analyses for former and recent users as well as for all metformin users regardless of duration of use. We also evaluated whether including women with less than 1-year metformin use altered the association between metformin and breast cancer risk. We repeated the analysis compared with women who used other antidiabetic medications only, as well as compared with women who were treated with diet and exercise only.

All statistical tests were 2-sided and all analyses were conducted using SAS (Version 9.1.3).

Results

We identified 393 breast cancer cases and 3,930 matched controls from the source population of 4,323 type 2 diabetic women. Table 1 shows the pattern of antidiabetic prescriptions received by cases and controls not accounting for duration of use. Twenty-two percent of cases and 20% of controls were not treated with any antidiabetic mediation before the index date. Most women had prescriptions for insulin or an oral antidiabetic medication, indicating that the majority of our population had more severe diabetes than women whose diabetes was managed with diet and exercise alone. In both case and control subjects, insulin was the most commonly prescribed antidiabetic medication. The majority of the subjects resided in Aarhus (36%) or North Jutland (42%) counties, which is a consequence of their larger populations and the longer duration of their prescription databases. Case subjects (58% $\geq$70 years old) were slightly older on average than control subjects (52% $\geq$70 years old), but they were similar in distribution for measured parity, use of hormone replacement therapy,

Table 1. Crude patterns of prescriptions for each antidiabetic medication by case and control status

Antidiabetic medication[a]	Cases				Controls			
	$n^b = 393$	# of prescriptions[c] (16,366)	Range of prescriptions[d] (1–552)	Years of use per person[e] (0.02–15.4)	$n^b = 3{,}930$	# of prescriptions[c] (173,358)	Range of prescriptions[d] (1–552)	Years of use per person[e] (0.01–19.2)
No prescriptions for at least 1 y	78	n/a	n/a	n/a	798	n/a	n/a	n/a
Insulin								
Fast acting	30	1,032	1–552	0.98–15.4	452	12,824	1–552	0.04–18.6
Intermediate acting	112	2,770	1–224	0.03–14.3	1,315	30,637	1–530	0.02–19.2
Intermediate, rapid onset	82	1,996	1–98	0.05–12.8	857	21,382	1–388	0.01–16.2
Other analogues, long acting	3	19	3–10	0.48–3.2	123	944	1–44	0.14–4.0
Metformin[f]	146	3,916	5–210	0.05–11.4	1,596	38,978	1–269	0.02–16.8
Sulfonamides	227	5,000	1–173	0.02–14.1	226	52,084	2–356	0.02–16.2
Combination	3	15	1–8	0.28–0.51	38	339	2–61	0.09–3.11
α-Glucoside inhibitors	19	301	1–106	0.05–7.5	185	2,383	1–163	0.01–10.9
Thiazolidinedine	2	17	2–15	0.02–1.5	31	395	1–57	0.03–7.7
Dipeptidyl peptidase 4 inhibitors	2	12	3–18	0.27–0.53	38	199	1–36	0.04–1.4
Other	5	63	1–38	0.19–2.5	76	1,134	1–113	0.02–6.8

[a]Prescriptions for each antidiabetic medication regardless of duration of use.
[b]Number of case and control subjects receiving any prescription for each antidiabetic medication. Cases and controls can use multiple types of medication.
[c]Total number of prescriptions for each antidiabetic medication does not take into account prescription product amount or unit size.
[d]Range of number of prescriptions per person does not take into account prescription product amount or unit size.
[e]Range of number of years prescribed per person regardless of duration of use.
[f]Number of case and control subjects include women with less than 1 year duration of metformin use.

Table 2. Distribution of descriptive characteristics by case and control subjects ($N = 4,323$)

Characteristic	Cases ($n = 393$)		Controls ($n = 3,930$)	
	n	%	*n*	%
Age at index date, y				
50–59	49	12	817	22
60–69	117	30	1,042	27
70–75	120	31	1,140	29
≥80	107	27	901	23
County				
Aarhus	142	36	1,420	36
North Jutland	165	42	1,650	42
Viborg	51	13	510	13
Ringkøbing	35	8.9	350	8.9
Year of birth				
Before 1920	77	20	667	17
1920–1939	226	58	1,997	51
1940–1959	90	23	1,266	32
Age at first birth, y				
Nulliparous	128	33	1,134	29
<20	30	7.6	328	9.4
20–29	127	32	1,503	39
≥30	74	19	549	14
Parity				
Nulliparous	128	33	1,134	29
1 child	82	21	798	20
2 children	95	24	1,007	26
3 children	58	15	617	16
≥4 children	30	7.6	374	9.5
Postmenopausal hormone replacement therapy	92	23	937	24
Polycystic ovarian syndrome	0	-	4	0.1
Diabetes complications	182	46	1,794	46
Time since diabetes diagnosis, y				
<5	172	44	1,724	44
5–10	106	27	962	24
≥10	115	29	1,244	32
Clinical obesity	50	13	628	16
Antidiabetic medication				
Metformin users[b]	96	24	1,154	29
Nonmetformin users[b]	297	76	2,776	71

[a]Metformin users were defined as women who were prescribed metformin for a minimum of 1-year duration and include women who used metformin and switched to other medications as long as they used metformin for at least 1 year.
[b]Nonmetformin users were defined as women not prescribed antidiabetic medications, women who were prescribed other antidiabetic medications, and women who did not use metformin for at least 1-year duration.

and history of diabetes complications (Table 2). Control subjects (16%) were slightly more often clinically obese than case subjects (13%). Women who used metformin for at least 1-year duration were younger, more likely to have used postmenopausal hormones, more often had diabetes complications, and were more often clinically obese than women who did not use metformin (Table 3). PCOS was rare ($n = 4$) and was recorded only among nonmetformin control subjects; therefore, we did not adjust for PCOS as a confounder of the association of metformin use and incident breast cancer. The distribution of women who used other antidiabetic medications was similar to the overall reference group. The women who were treated with a diet and exercise regimen only were more recently diagnosed with type 2 diabetes and were less likely to have diabetes complications (Table 3).

Table 3. Descriptive characteristics by metformin, nonmetformin, other antidiabetic medications, and no antidiabetic medications ($N = 4,323$)

Characteristic	Metformin[a] ($n = 1,250$)		Nonmetformin[b] ($n = 3,073$)		Other antidiabetic medications only[c] ($n = 2,197$)		Diet and exercise only[d] ($n = 876$)	
	n	%	*n*	%	*n*	%	*n*	%
Age at index date, y								
50–59	307	25	589	19	386	18	203	23
60–69	428	34	731	24	530	24	201	23
70–75	336	27	924	30	683	31	241	28
≥80	179	14	829	27	598	27	231	26
County								
Aarhus	473	38	1,089	35	743	34	346	40
North Jutland	510	41	1,305	42	970	44	335	28
Viborg	151	12	410	13	306	14	104	12
Ringkøbing	116	9.3	269	8.8	178	8.1	91	10
Year of birth								
Before 1920	103	8.2	641	21	452	21	189	22
1920–1939	632	51	1,591	52	1,193	54	398	45
1940–1959	515	41	841	27	552	25	289	33
Age at first birth, y								
Nulliparous	277	22	985	32	715	33	270	31
<20	158	13	200	6.5	146	6.7	54	6.2
20–29	541	43	1,089	35	770	35	319	36
≥30	142	11	481	16	346	16	135	15
Parity								
Nulliparous	277	22	985	32	715	33	270	31
1 child	220	18	660	21	492	22	168	19
2 children	343	27	759	25	511	23	248	28
3 children	254	20	421	14	293	13	128	15
≥4 children	156	12	248	8.1	186	8.5	62	7.1
Postmenopausal hormone therapy	328	26	701	23	516	24	185	21
Polycystic ovarian syndrome	0	–	4	0.2	2	100	2	100
Diabetes complications	601	48	1,375	45	1,146	52	229	26
Clinical obesity	338	27	340	11	219	10	121	14
Time since diabetes diagnosis, y								
<5	462	37	1,434	47	919	42	515	59
5–10	428	34	640	21	494	22	146	17
≥10	360	29	999	33	784	36	215	25

[a]Metformin users were defined as women who were prescribed metformin for a minimum of 1-year duration and include women who used metformin and switched to other medications as long as they used metformin for at least 1 year.
[b]Nonmetformin users were defined as women who were not prescribed antidiabetic medications, women who were prescribed other antidiabetic medications, and women who did not use metformin for at least 1-year duration.
[c]Women who were prescribed other antidiabetic medications for a minimum of 1-year duration.
[d]Women treated with diet and exercise only (no prescriptions for antidiabetic medications).

Ninety-six cases (24%) and 1,154 controls (29%) used metformin for at least 1-year duration (Table 2). Metformin users were less likely to be diagnosed with breast cancer (OR = 0.77; 95% CI = 0.61–0.99) than women who used other oral and injectable antidiabetic medications or no medication (Table 4). Adjustment for complications due to diabetes occurring before the index date (OR = 0.77; 95% CI = 0.60–0.98), in addition to clinical obesity before the index date (OR = 0.82; 95% CI = 0.64–1.08), and important predictors of breast cancer (OR = 0.81; 95% CI = 0.63–0.96) did not substantially alter the association between metformin exposure and incident breast cancer.

Table 4. Associations between metformin medication and incident breast cancer in a prospective population-based study ($N = 4,323$)

Exposure categories	Cases ($n = 393$)	Controls ($n = 3,930$)	Conditioned on county[a]		Adjusted for diabetes complications and clinical obesity[b]		Multivariable adjusted[c]		Multivariable adjusted imputed parity[d]	
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
No metformin	297	2,776	1.00	–	1.00	–	1.00	–	1.00	–
Metformin[f]	96	1,154	0.77	0.61–0.99	0.82	0.64–1.08	0.82	0.64–1.08	0.81	0.63–0.96
Former[g]	15	196	0.71	0.41–1.23	0.73	0.42–1.27	0.72	0.41–1.26	0.72	0.42–1.26
Recent[h]	81	958	0.78	0.60–1.01	0.81	0.61–1.06	0.84	0.64–1.10	0.83	0.63–1.08
5-y metformin duration	35	418	0.75	0.51–1.09	0.78	0.54–1.15	0.82	0.56–1.21	0.83	0.56–1.22
Other medications	219	1,978	1.00	–	1.00	–	1.00	–	1.00	–
Metformin[f]	96	1,154	0.74	0.57–0.96	0.76	0.58–0.99	0.78	0.60–1.03	0.78	0.59–1.01
Former[g]	15	196	0.64	0.37–1.12	0.66	0.38–1.15	0.64	0.37–1.12	0.81	0.61–1.08
Recent[h]	81	958	0.76	0.58–1.00	0.78	0.59–1.03	0.82	0.62–1.09	0.64	0.36–1.12
5-y metformin duration	35	418	0.71	0.48–1.06	0.74	0.50–1.11	0.80	0.53–1.20	0.80	0.53–1.31
Diet and exercise only[e]	78	798	1.00	–	1.00	–	1.00	–	1.00	–
Metformin[f]	96	1,154	0.89	0.64–1.24	0.88	0.62–1.25	0.87	0.60–1.24	0.87	0.61–1.25
Former[g]	15	196	0.96	0.52–1.79	0.92	0.48–1.74	0.82	0.43–1.59	0.85	0.44–1.64
Recent[h]	81	958	0.88	0.62–1.24	0.88	0.61–1.25	0.87	0.60–1.26	0.87	0.60–1.26
5-y metformin duration	35	418	0.80	0.48–1.32	0.78	0.46–1.33	0.72	0.41–1.27	0.74	0.43,1.29

[a]Conditional logistic regression used to adjust for confounding and selection bias introduced by matching on county.

[b]Conditional logistic regression used to adjust for confounding and selection bias introduced by matching on county and adjusting for complications due to diabetes and clinical obesity.

[c]Conditional logistic regression used to adjust for confounding and selection bias introduced by matching on county and adjusting for complications due to diabetes, clinical obesity, age at index date, postmenopausal hormone use, and parity at index date.

[d]Conditional logistic regression used to adjust for confounding and selection bias introduced by matching on county and adjusting for complications due to diabetes, clinical obesity, age at index date, postmenopausal hormone use, and multiple imputation to impute missing parity.

[e]Women who were treated with a diet and exercise regimen only.

[f]Metformin users were women who used metformin for a minimum of 1-year duration.

[g]Former users were women whose last metformin prescription was greater than 1 year from the index date.

[h]Recent users were women whose last metformin prescription was within 1 year before the index date.

Type 2 diabetic women with 5 years of metformin use had approximately 20% reduction in breast cancer rate compared with women using other antidiabetic medications (OR = 0.83; 95% CI = 0.56–1.22). The strongest inverse association between metformin users and breast cancer was observed among women with diabetes complications (OR = 0.67; 95% CI = 0.45–1.01). The results did not change appreciably among women without complications (OR = 0.84; 95% CI = 0.59–1.21) compared with nonmetformin users or when exposure was restricted to recent users (OR = 0.83; 95% CI = 0.63–1.08). Former users had a slightly stronger effect on breast cancer risk than nonmetformin users (OR = 0.72; 95% CI = 0.42–1.26), but only 15 exposed cases contributed to this finding. Restricting exposure to metformin monotherapy did not appreciably change the association (OR = 0.82; 95% CI = 0.64–1.05). However, the association nearly disappeared when we defined metformin users as only those women who used metformin for less than 1 year (OR = 0.93; 95% CI = 0.74–1.17). The results did not materially change when we compared metformin users with other antidiabetic medication users only (adjusted metformin OR = 0.78; 95% CI = 0.60–1.03; Table 4), but the association was attenuated when we compared metformin with a diet and exercise regimen only (adjusted metformin OR = 0.87; 95% CI = 0.60–1.24; Table 4). We found that sulfonamide prescriptions were disproportionately redeemed in cases than in controls (Table 1). However, sulfonamide, compared with diet and exercise only, was not associated with breast cancer when we accounted for matching on county (OR = 1.01; 95% CI = 0.57–1.79).

Discussion

Our study is the largest to report on the association between metformin use and incident breast cancer in a type 2 diabetic population as the primary study objective. Consistent with earlier findings of the association between metformin use and risk of any cancer (11, 12), we observed approximately a 20% reduction in the rate of incident invasive breast cancer among type 2 diabetic women using metformin compared with both nonmetformin users and other antidiabetic medication users only. Our results were robust to varying definitions of exposure such as recent use, duration, and metformin monotherapy, were stronger among former metformin users, and strongest when restricted to women with diabetes complications. However, the association was attenuated when we compared metformin users with diabetic women managed by diet and exercise only. These nonprescription users were more recently diagnosed with diabetes and had a lower proportion of diabetes complications, which suggests that the comparison of metformin users with diabetes managed by only diet and exercise may be confounded by indication.

Selection bias is an unlikely explanation for our findings because we used the Danish National Registry of Patients as the source for our diabetic population, from which the controls were randomly selected, independent of metformin exposure (18). Misclassification of disease status is also unlikely because the Danish Cancer Registry has near-perfect completeness for breast cancer diagnoses (17).

The plausibility of our results for a reduction in breast cancer risk is supported by the 2 population-based studies by Libby et al. and Bodmer et al. (11, 12). In addition, our results are supported by laboratory studies, in which metformin reduces hepatic glucose output and may reduce cell proliferation in at-risk epithelial cells (9). Only 24 women used metformin and developed breast cancer in the study by Libby et al., but metformin users had a 40% decreased risk of breast cancer compared with nonusers after adjusting for age, smoking status, socioeconomic status, body mass index, hemoglobin A_{1c} (HbA_{1c}), insulin use, and sulfonylureas use (11). However, in the study of Libby et al., obesity and diabetes complications were measured after first exposure to metformin (11). Therefore, in the study of Libby et al., measurements of obesity (body mass index) and diabetes complications (HbA_{1c}) over the study period may have been influenced by metformin treatment and so may be on the causal pathway rather than confounding the relation between metformin and cancer risk. We observed that the inverse association in our study persisted even after adjusting for complications due to diabetes before the index date, for clinical obesity before the index date, and for other breast cancer risk factors.

Bodmer et al. observed a 56% reduction in breast cancer risk for women with 5 or more years of metformin use, compared with nonmetformin use, but a null to weak association with fewer years of use (12). Similar to Bodmer et al., we observed that women with 5 or more years of metformin use had a decreased risk of breast cancer and that short-term users did not. Our results differ from the finding of Currie et al. (5), which found no association between metformin use compared with using sulfonylureas only and breast cancer risk, which may be explained by differences in the exposure definitions. Currie et al. defined exposure as 6 months of treatment (5), whereas we required 1 year duration. When we included women with less than 1-year duration of metformin as exposed, the association between metformin and breast cancer risk nearly disappeared, suggesting that a minimum of 1-year induction period may be required to detect an inverse association between metformin and breast cancer risk.

Although our results suggest metformin protects against breast cancer in type 2 diabetic women 50 years or older, they should be viewed with the following limitations in mind. The Danish National Registry of Patients and county prescription databases do not collect anthropometric measurements such as weight, height, waist circumference, or hip circumference. However, confounding by obesity should work in the causal direction, as obesity increases the risk of breast cancer (24–26) and is an indication for

metformin use in diabetic patients (27). Consequently, if our result is biased by confounding by obesity, adjustment for obesity should result in an even more protective effect of metformin on the risk of breast cancer than we reported, perhaps as strong as the 40% protection observed by Libby et al. (11) and 56% protection for 5-year duration of metformin observed by Bodmer et al. (12).

Not all antidiabetic medications offer similar tumor-suppressing effects as metformin. Some insulin medications—specifically glargine—have been associated with breast cancer risk in some studies (28), but other forms of insulin have been observed to have a null association (29) irrespective of the dose or duration (30, 31). If insulin is truly positively associated with breast cancer risk, we would expect that mixing women who used metformin plus insulin in our exposure definition would bias our result toward the null, because the insulin association would work in the opposite direction of the metformin association. However, we observed a similar decrease in breast cancer risk when we restricted to metformin monotherapy users, suggesting our results were unaffected by combining women who used metformin plus insulin in our exposure definition.

Finally, because the prescription databases started after the Danish National Registry of Patients, there may be left truncation of information about metformin exposure. We could have misclassified time exposed to metformin as time not exposed. In addition, there may be a subset of women who did not meet the 1-year duration of metformin use to be considered exposed but actually could have met this exposure criterion if the database contained prescription information from earlier times. Left truncation would result in nondifferential misclassification of exposure and would bias the dichotomous results toward the null. By using the prescription databases as our source for exposure information, we assumed that redemption of prescriptions for medications is equivalent to actually using medications. Metformin is used to treat diabetes, a serious disease, and patients who redeem prescriptions are reimbursed for only part of the cost. Prescription redemption is therefore a sound surrogate for actually taking the medications, particularly when a patient redeems more than 1 prescription. Because the prescription information was recorded before the breast cancer diagnosis, any classification errors from this source of misclassification would also be nondifferential and bias the dichotomous association toward the null.

Our results support the finding of Libby et al. and the preliminary evidence of Bodmer et al., showing metformin, compared with nonmetformin, reduces the risk of breast cancer (11, 12). In addition, our results are indirectly supported by observational studies of diabetic patients who used metformin having a decreased risk of all cancers (5, 11) compared with patients who used other antidiabetic medications, as well as laboratory studies suggesting a mechanism by which metformin use might inhibit breast cancer cell growth (32, 33). Our data support the hypothesis that metformin may be a candidate agent for breast cancer prevention. We studied a population of type 2 diabetic women because metformin reduces insulin levels only in those with elevated concentrations. Thus, the relevance of our findings in nondiabetic populations is unknown.

This preliminary evidence, in concert with findings of our study, supports the notion that metformin reduces the risk of breast cancer in type 2 diabetic peri- and postmenopausal women.

Disclosure of Potential Conflicts of Interest

H.T. Sørensen did not report receiving fees, honoraria, grants, or consultancies. Department of Clinical Epidemiology is, however, involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. One of these studies is an international consortium studying the effects of diabetic medications on the occurrence of multiple cancers, including breast cancer. The study is sponsored by a manufacturer of diabetic medications (Sanofi-Aventis). The design, analysis, and draft presentation of this study were completed before the international study began, and the international study provided no support for this study. No declared conflicts of interest from J.L.F. Bosco, S. Antonsen, L.A. Pedersen, or T.L. Lash.

Appendix

Appendix A: List of ICD 8th and 10th Revision Codes Used to Identify Key Diagnoses

Diagnosis	ICD-8	ICD-10
Type 2 diabetes	250	E11
Invasive breast cancer	174.00–174.02; 174.08; 174.09	C50.0–C50.6; C50.8
Diabetes complications	249.01; 250.01; 377.00; 249.02; 250.02; 792.99; 249.03; 250.03; 410; 431; 433; 434; 436; 249.04; 250.04; 440.20; 440.28; 440.29; 440.99	E10.2–E10.5; E11.2–E11.5; E14.2; E14.3; E14.5; G62.9; G63.2; H10.2; H33.4; H36.0; H43.1; H45.0; I61; I63; I64; I70.2; I70.9; N08.3; N18; N19
Clinically diagnosed obesity	n/a	E66; E66.1; E66.2; E66.8; E66.9
Polycystic ovarian syndrome	256.9	E28.2

Appendix B: List of ATC Codes Used to Identify Prescriptions for Key Medications

Prescription	ATC code(s)
Hormone replacement therapy	G03A; G03C; G03D; G03F; G03G; G03X; L02A
Insulin	
Fast acting	A10AA01; A10AB01; A10AB04; A10AB05
Intermediate acting	A10AA02; A10AC01
Intermediate, rapid onset	A10AA03; A10AD01; A10AD04; A10AD05
Other analogues, long acting	A10AE; A10AE04; A10AE05
Metformin	A10BA02; A10BD02; A10BD03; A10BD05
Sulfonamides	A10BB01–A10BB03; A10BB07; A10BB09; A10BB12
Combination	A10BD03
α-Glucoside inhibitors	A10BF01
Thiazolidinedine	A10BG01; A10BG03
Dipeptidyl peptidase 4 inhibitors	A10BH01
Other	A10BX02

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