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ORIGINAL PAPER

Associations of type 2 diabetes and diabetes treatment with breast cancer risk and mortality: a population-based cohort study among British women

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Abstract
Purpose There is great interest in whether type 2 diabetes and its treatments alter breast cancer risk and prognosis, but previous studies are inconclusive. We conducted a cohort study within the UK General Practice Research Database to investigate associations of type 2 diabetes and patterns of diabetes treatment with breast cancer risk and all-cause mortality.
Methods We identified 52,657 women with type 2 diabetes, diagnosed between 1987 and 2007, and 30,210 randomly selected women without diabetes. We performed a time-dependent analysis using Cox proportional hazards models.
Results Diabetes was associated with a 29 % increased overall breast cancer risk (95 % CI: 1.16–1.44), but the association markedly attenuated when adjusted for age, period of cohort entry, region, and body mass index (BMI) (HR: 1.12; 95 % CI: 0.98–1.29). Women with breast cancer and pre-existing diabetes had a 49 % (95 % CI: 1.17–1.88) increased all-cause mortality risk compared with women with breast cancer but without diabetes, after controlling for age, period, region, BMI, smoking, alcohol, and deprivation. Compared with sulfonylurea, we found weak evidence that metformin monotherapy (HR: 1.04; 95 % CI: 0.79–1.37) and insulin (HR: 1.33; 95 % CI: 0.63–2.83) modified breast cancer risk among women with diabetes.
Conclusions We found weak evidence that diabetes is associated with a small increased risk of breast cancer. Among treated women, there is no evidence that anti-diabetes treatments modify the risk of developing breast cancer, with wide confidence intervals indicating imprecise effect estimates. Women with breast cancer and diabetes, however, had an increased all-cause mortality risk highlighting the potential importance of maintaining adequate glycemic control alongside anti-cancer treatments and subsequent follow-up.

Keywords Diabetes · Diabetes treatment · Breast cancer risk · GPRD · British women

Introduction

Several epidemiological studies have investigated the association between diabetes and breast cancer. A meta-analysis of 26 studies, involving nearly 1 million women, found that those with diabetes had a 15 % increased risk of subsequent breast cancer (pooled relative risk, RR: 1.15; 95 % confidence interval, CI: 1.12–1.19) [1]. Another meta-analysis of 20 studies found similar results (pooled RR: 1.20; 95 % CI: 1.12–1.28) [2]. The effect was stronger for post- (pooled RR: 1.19; 95 % CI: 1.15–1.23) compared with pre- (pooled odds ratio, OR: 0.94; 95 % CI: 0.80–1.10) menopausal breast cancer [1] (p for difference in effect estimates = 0.002).

Possible pathways through which type 2 diabetes could affect breast cancer risk include direct effects of hyperinsulinemia, hyperglycemia, or the insulin-like growth factor (IGF) system on stimulating cell proliferation and

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inhibition of apoptosis and indirect effects mediated through altered levels of sex hormones [3–8]. Epidemiological studies, combined with evidence from mouse models [9], have led to concerns that treatments which elevate circulating insulin in people with diabetes might potentially confer an increased risk of cancer [7]. Furthermore, it has been suggested that insulin analogues, such as insulin glargine, may be associated with a higher risk of cancer than human insulin [7] in some [10, 11] but not all studies [12].

On the other hand, metformin reduces hepatic glucose output, indirectly lowering circulating insulin in diabetes [13], and, at the cellular level, increasing the AMP-activated protein kinase (AMPK) signaling pathway, inhibiting the downstream mitogenic pathway, mammalian target of rapamycin (mTOR) [14]. In line with these physiologic effects, a limited number of epidemiological studies have found a 19–66 % decreased risk of breast cancer with metformin compared with other or no treatment [15–17], possibly limited to long-term use [15]. However, not all studies found evidence to support such an association [18–20].

The effects of diabetes on all-cause mortality after cancer diagnosis are less well studied, but an increased risk is plausible via dysregulated growth hormones, hyperinsulinemia or activation of IGFs, and insulin receptors (IR) [1, 21]. A meta-analysis found that all-cause mortality among breast cancer patients with pre-existing diabetes was 49 % higher than those without diabetes (pooled Hazard Ratio, HR: 1.49; 95 % CI: 1.35–1.65) [22], supported by a recent British study that showed a 32 % increased all-cause mortality risk among breast cancer patients associated with type 2 diabetes (HR: 1.32; 95 % CI: 1.17–1.49) [23] and a Swedish study that showed a 45 % increased cause-specific mortality risk (HR: 1.45; 95 % CI: 1.32–1.59) [24].

We conducted a large historical cohort study within the UK General Practice Research Database (GPRD) to investigate associations of type 2 diabetes and its treatment with overall, pre-menopausal and postmenopausal breast cancer incidence, and all-cause mortality among women diagnosed with breast cancer. The frequent use of multiple treatments in diabetes makes defining mutually exclusive exposure groups problematic. Comparing ever versus never users of each drug class (e.g., ever vs never metformin) may introduce confounding by drugs that were used in combination or that were switched (e.g., ever metformin users would include some of those who, at the same treatment stage, were also exposed to insulin and sulfonylurea). In our study, we compared mutually exclusive groups and defined exposure based on each individual's treatment pattern, which may have been no drug therapy, sole therapy, combination therapy, or involved a pattern of switching.

Materials and methods

Data sources

Data for this analysis came from the GPRD, a large computerized database of anonymized primary care medical records [25]. It currently includes prospectively gathered administrative, clinical, and prescribing records (including all consultations and diagnoses) for about 5 million active patients from over 600 primary practices throughout the UK, equating to 7 % of the population [25]. Individuals registered on the database are representative of the age, sex, and geographical distribution of the UK population [26]. Data are subject to thorough validation, audit, and quality checks [27, 28], and there is a high level of diagnostic validity for breast and other cancers [25, 29] and endocrine/metabolic diseases [27].

Study population

The study was conducted in a cohort of women who were registered in the GPRD between 1 January 1987 and 31 December 2007. Date of cohort entry was defined as 12 months after the practice up-to-standard date or the date the patient was registered with the practice, whichever came later. The up-to-standard date is the starting date at which the practice is considered to have continuous high-quality data [30]. Data are considered to be up to research standard if, following audit and quality checks, they are approved by the GPRD as being of high quality that is fit for use in research.

The exposed group was defined as women with diabetes diagnosed at or after the age of 35 years between 1 January 1987 and 31 December 2007. Diabetes was defined as follows: a diagnosis of non-insulin dependent or diabetes of unspecified type, or a prescription of insulin (British National Formulary, BNF, Chapter 6.1.1) or at least two prescriptions of oral hypoglycemic drugs (BNF Chapter 6.1.2). For the last criterion, the date of diabetes diagnosis was based on the date of the second prescription, regardless of the time between the prescriptions. Exclusion criteria were a diagnosis of insulin-dependent diabetes mellitus or gestational diabetes mellitus at any time in the medical records. To ensure only incident cases were included, women with a diagnosis of type 2 diabetes (based on our definitions) prior to their date of cohort entry (see above for definition) were also excluded. All women were also required not to have had any type of diabetes or a breast cancer diagnosis and not to have been taking insulin or any oral hypoglycemic drug at any time prior to their date of cohort entry. Of the initial 62,638 diabetes patients that were identified in the GPRD, 5,302 were excluded based on the inclusion criteria, 4,255 do not have at least

12 months of follow-up prior to diabetes diagnosis, and 424 cannot be confirmed as a case based on the definitions. A total of 52,657 cases were left for the analysis.

The 30,210 unexposed patients were a random sample of GPRD-registered women who were at least 35 years of age, never had a diagnosis of diabetes, had never taken insulin or any oral hypoglycemic drug and were free from breast cancer at the time of cohort entry. They were frequency-matched to the exposed subjects by year of birth and GP practice.

Diabetes treatments

Using the British National Formulary codes (http://bnf.org), diabetes therapy was classified as insulin (Chapter 6.1.1.1 and 6.1.1.2), sulfonylurea (Chapter 6.1.2.1), metformin (Chapter 6.1.2.2), and other oral hypoglycemic drugs, which included rosiglitazone, pioglitazone, acarbose, exenatide, neteglinide, repaglinide, and sitagliptin (Chapter 6.1.2.3). A patient was considered exposed to each of the above treatments if they had continuous prescriptions of a particular drug lasting at least 6 months, to exclude prescribing errors and ensure sufficient exposure to influence breast cancer development. The dates of the first and last prescription for each drug were determined, and any overlaps indicating combination therapy were assessed. Gaps in the prescriptions were noted, and a new prescription of a particular drug 6 months after the last prescription was treated as a new regimen. The date of the start of treatment was defined as the date of the first prescription for any drug.

Treatment patterns for the entire duration of follow-up were then identified by the chronological order of drug prescriptions. An individual's treatment pattern was categorized into one of the following mutually exclusive groups: (1) monotherapy with either insulin, sulfonylurea, or metformin, if they were only ever exposed to one of these drugs (or one of these drugs was in combination with those drugs classified as "other", which form only a small percentage of the drugs given for diabetes); (2) therapy with sulfonylurea and metformin, either one of these two agents followed sequentially by the other, or with these agents prescribed in combination; (3) individuals who were treated with sulfonylurea and/or metformin followed by insulin; and (4) any other drug combinations.

Covariables

Age at cohort entry was categorized as less than 40, 40–49, 50–59, 60–69 and 70 years and above. As menopausal status is not directly recorded on the GPRD and with the age of 49 reported as the median age of menopause among British women [31], postmenopausal breast cancer was defined as those cancers occurring on or after the age of 50 years. To account for temporal changes in diagnostic and treatment practices, period of cohort entry, categorized in 5-year time bands as 1987–1991, 1992–1996, 1997–2001, and 2002–2007, and year of diabetes diagnosis were included as covariables in the analysis. Geographical variability in practices was also taken into consideration by controlling for region of GP practice.

Body mass index (BMI) was based on the first measurement after cohort entry. It was categorized as underweight, normal, overweight, and obese ($<$18.5, 18.5–24.9, 25–29.9, and $\geq$30 kg/m^2, respectively). Alcohol drinking and smoking status were defined as status at cohort entry (never smoker or drinker, ex- and current). Hormone replacement therapy (HRT) was the number of prescriptions for the duration of follow-up, categorized as having received none, 1–19 or 20 or more prescriptions.

Level of deprivation was based on the Index of Multiple Deprivation (IMD) score calculated for each individual. The IMD score is a composite measure covering income, employment, health, education, housing, living environment, and crime for small geographical areas known as Lower Super Output Areas (LSOAs) [32]. Each LSOA is comprised of a minimum population of 1,000 and represents the woman's neighborhood of residence. Quintiles based on the scores were computed with the first quintile designated as the least deprived.

Glycemic control was defined as a time-weighted average of glycosylated hemoglobin (HbA1c) levels. All HbA1c measurements from the time of first prescription for diabetes to end of follow-up were determined. The time-weighted mean HbA1c value was computed, with each value weighted by the length of time between measurements. Due to the large proportion of all patients with diabetes who did not have HbA1c measurements (33.82 %), HbA1c was only taken into consideration for the analysis of treatment pattern effects among patients who received insulin or oral hypoglycemic drugs, where a larger proportion (91.19 %) had measurements recorded.

To account for missing data on BMI, alcohol drinking, smoking, IMD score, and HbA1c, multiple imputation using chained equations (ICE) was employed [33]. For each missing variable, imputation models were derived. These models included the following: the exposure of interest (diabetes status or diabetes treatment pattern); the incomplete variables; other covariables (age, period, region, use of HRT, year of diabetes diagnosis); possible factors related to the variables with missing information (systolic and diastolic blood pressure, number of GP consultations per year, use of oral contraceptives, intake of medications for cardiovascular disease (CVD), gastro-esophageal diseases or obesity, a diagnosis of hypertension, CVD, or weight problems); and outcome (breast cancer

status or all-cause mortality and person-years of follow-up). A total of 20 complete datasets were constructed to reduce sampling variability from the imputation process [34]. The distributions of the imputed variables were similar to the distributions of the measured variables.

Data analysis

To assess the potential for confounding in the association of diabetes with breast cancer, associations of age, BMI, smoking, alcohol drinking, HRT, level of deprivation, and HbA1c with diabetes status and breast cancer were determined using the chi-square test and Cox proportional hazards models, respectively. To assess the association of type 2 diabetes with breast cancer risk, Cox proportional hazards models were used, with women who did not have diabetes as the reference group and controlling for the effects of co-variables associated with diabetes and breast cancer, period of cohort entry, and region of GP practice. Associations were stratified by pre- and postmenopausal breast cancer status, and the statistical significance of the difference between these stratified effect estimates were determined [35]. Since only a proportion of women without diabetes were randomly selected as unexposed, weights were used in the analysis, defined as the probability of women in the GPRD population being selected into the study.

In the analysis of the association of type 2 diabetes with breast cancer risk, women were followed up from the date of cohort entry to the date of diagnosis of breast cancer, death, transfer out of (leaving) the practice, or date of the practice no longer being up-to-standard, whichever came first. To avoid immortal time bias among patients with diabetes (the exposed), we used the time-dependent analysis suggested by Levesque and colleagues [36]. The duration of time without diabetes for the exposed group was calculated as the difference between the date of diabetes diagnosis and the date of cohort entry. This was then assigned to the unexposed group instead of the group with diabetes (Fig. 1).

A complete case analysis was done to check the assumption that data were missing at random (MAR). A sensitivity analysis, excluding the first 2 years immediately after diabetes diagnosis (for cases) and first 2 years after cohort entry (for controls), was also carried out to check for ascertainment bias. If the assumption of MAR was correct and if there is no ascertainment bias, the results of the complete case and sensitivity analyses would be similar to the results of the Cox regression.

Among women diagnosed with breast cancer, the association of type 2 diabetes with all-cause mortality was determined, while controlling for age, period, region, alcohol drinking, smoking status, HRT, and level of deprivation. Cause-specific mortality could not be determined as cause of death was not available in the dataset. In this analysis, women were followed up from date of breast cancer diagnosis, to the date of death, transfer out of the practice, or date of the practice no longer being up-to-standard, whichever came first.

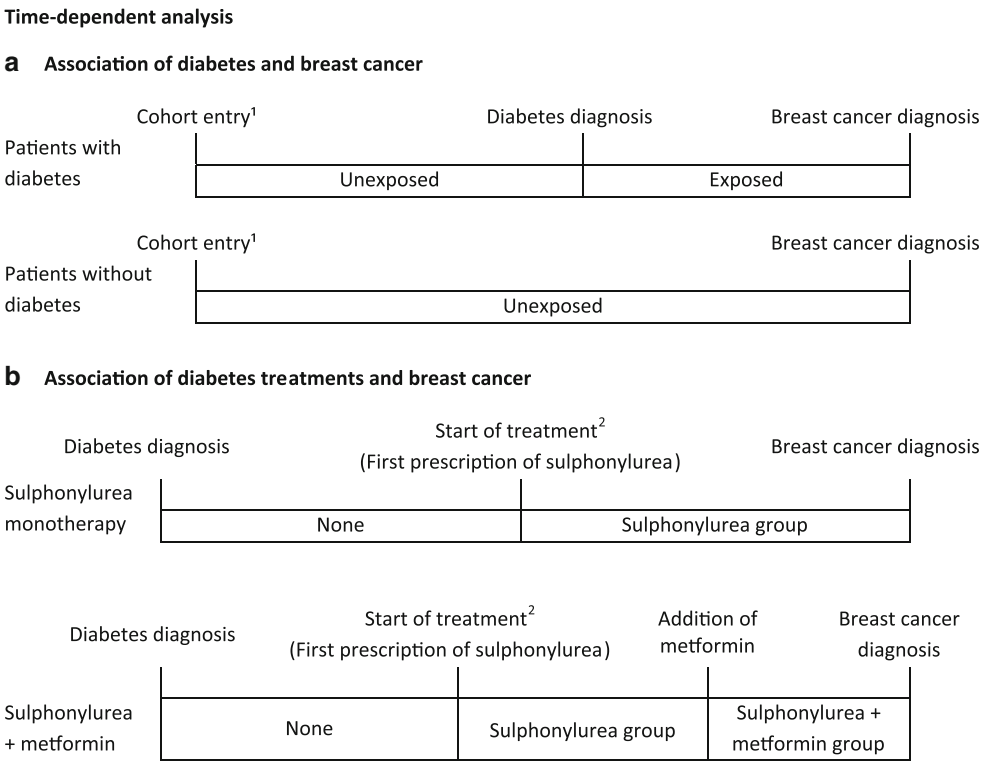

Fig. 1 Illustration of the time-dependent analysis. **a** Person-years prior to index date was assigned to the unexposed group. **b** Person-years after index date prior to prescription of any oral anti-diabetes drug or insulin was assigned to the "none" group. Initial monotherapy person-years were assigned to the monotherapy group. [1]Cohort entry is defined as 12 months after the practice up-to-standard date or the date the patient was registered into the practice, whichever came later. [2]The start of treatment was defined as the date of the first prescription for any drug

Among women with diabetes, Cox proportional hazards models were used to calculate associations of each pre-defined treatment pattern (insulin monotherapy; sulfonylurea monotherapy; metformin monotherapy; sulfonylurea and metformin; sulfonylurea and/or metformin followed by insulin; other) with overall breast cancer risk. Women receiving sulfonylurea therapy only were designated as the reference group due to the large number of patients in this group and because previous studies found no association of sulfonylurea with breast cancer risk [15, 18, 19]. By comparing people who are treated, we should reduce potential confounding by indication, that is, people who were treated pharmacologically were different from those not pharmacologically treated (e.g., in terms of severity). The effects of covariables associated with breast cancer, period, region, and the year of diabetes diagnosis were controlled for in the analysis.

Treatment exposures were classified up until the date of the event (diagnosis of breast cancer, death, and transfer out of the practice or date of practice no longer up-to-standard). Several patients will have contributed to several exposure groups because of the way exposure was classified in order to avoid immortal time bias [19]. To illustrate, if a person started with sulfonylurea monotherapy then took metformin in combination with sulfonylurea after 4 months, the initial four person-months sulfonylurea monotherapy was assigned to the sulfonylurea group, while the succeeding person-years was assigned to the sulfonylurea plus metformin group (Fig. 1).

A separate analysis including only women who received insulin or oral hypoglycemic drugs and controlling for time-weighted HbA1c level, as a measure of diabetes severity, was also undertaken. It is implausible that drugs initiated just before diagnosis of breast cancer could actually cause the cancer. We therefore performed analyses to examine a latency period, by excluding prescriptions either 6 months or 3 years prior to cancer diagnosis or censoring. There were not enough women with breast cancer to assess associations of treatments for diabetes with mortality outcomes.

For each variable included in the Cox models, the assumption of proportional hazards was checked using Nelson–Aalen plots. Insulin treatment violated this assumption mainly due to the small numbers of breast cancer cases. To take this violation into account, treatment period was divided into <1, 1–5, and >5 years after treatment initiation. All analyses were undertaken using Stata version 12.1 [37].

Results

Table 1 shows the baseline characteristics of the study cohort. More women with type 2 diabetes (81.1 %) were overweight or obese compared with women without diabetes (53.9 %). There were only small differences in the distributions of women with and without diabetes by age, smoking, drinking, estrogen use, and deprivation, even though, because of large numbers, the p values were very small. Among women with diabetes, we identified 873 women with breast cancer, 143 with pre-menopausal breast cancer, and 730 with postmenopausal breast cancer. Among those without diabetes, we identified 714 women with breast cancer, 137 with pre-menopausal breast cancer, and 577 with postmenopausal breast cancer. Table 2 shows the unadjusted and age, period, and region-adjusted hazard ratios of the association of the different covariables with breast cancer risk. Being obese was associated with an increased risk of breast cancer.

In a crude model, type 2 diabetes was associated with a 29 % increased risk of overall breast cancer (95 % CI: 1.16–1.44) compared with women without type 2 diabetes (Table 3), but the magnitude of the association was attenuated when adjusted for age, period, region, and BMI (HR: 1.12; 95 % CI: 0.98–1.29; $p = 0.10$). Being a woman with type 2 diabetes was not associated with pre-menopausal breast cancer (HR: 1.01; 95 % CI: 0.46–2.22; $p = 0.99$) but was associated with an increased risk of postmenopausal breast cancer (HR: 1.13; 95 % CI: 0.98–1.29; $p = 0.09$). However, there was no statistical evidence that the association of diabetes with breast cancer differed by menopausal status (p for heterogeneity in effect estimates = 0.79). The results of the complete case and sensitivity analyses (data not shown) did not differ from the results presented in Tables 2 and 3.

Among patients with breast cancer, women with type 2 diabetes had a twofold increased all-cause mortality risk compared with women without type 2 diabetes (HR: 2.14; 95 % CI: 1.77–2.60), but this association was attenuated after controlling for age, period, region, alcohol drinking, smoking status, HRT, and level of deprivation (HR: 1.49; 95 % CI: 1.17–1.88; $p = 0.001$).

Of women with diabetes, 48.7 % received no prescriptions of insulin or oral hypoglycemic drugs, 22.6 % were prescribed metformin, while 9.1 % were prescribed sulfonylurea (Table 4). Women classified in the combined sulfonylurea and metformin category accounted for 14.1 % of all those with diabetes. Only 4.0 % of patients were switched from oral hypoglycemic drugs to insulin therapy, while only 0.8 % of patients were prescribed insulin as sole therapy. Among all women with diabetes, we found little evidence that insulin was associated with breast cancer risk in the crude (HR: 1.03; 95 % CI: 0.49–2.17) or multivariable-adjusted (HR: 1.14; 95 % CI: 0.54–2.39) models when compared with women categorized as receiving sulfonylurea therapy only (Table 5). Neither was there evidence that metformin was associated with breast cancer

Table 1 The distribution of patients with risk factors

Variable	Patients without diabetes $n = 30,210$		Patients with diabetes $n = 52,657$		Chi-square p value[a]
	n	%	n	%	
Age group					<0.001[b]
<40	1,179	3.90	3,095	5.88	
40–49	4,675	15.48	9,337	17.73	
50–59	7,508	24.85	13,102	24.88	
60–69	8,324	27.55	14,338	27.23	
70 and above	8,524	28.22	12,785	24.28	
BMI					<0.001[2]
Underweight (<18.5)	477	2.61	197	0.72	
Normal (18.5–24.9)	7,947	43.52	4,979	18.23	
Overweight (25–30)	6,280	34.39	9,137	33.46	
Obese (≥30)	3,557	19.48	12,995	47.59	
Total with data	18,261	100.00	27,308	100.00	
Missing	11,949	39.55[c]	25,349	48.14[d]	
Smoking status					<0.001
Non	13,562	62.94	17,684	60.40	
Current	4,316	20.03	6,967	23.80	
Past	3,671	17.04	4,625	15.80	
Total with data	21,549	100.00	29,276	100.00	
Missing	8,661	28.67[c]	23,381	44.40[d]	
Drinking status					<0.001
Non	3,956	24.78	6,839	29.02	
Current	11,743	73.55	16,370	69.47	
Past	268	1.68	355	1.51	
Total with data	15,967	100.00	23,564	100.00	
Missing	14,243	47.15[c]	29,093	55.25[d]	
Estrogen use					<0.001[b]
None	24,112	79.81	46,414	82.82	
1–19	3,522	11.66	6,188	11.04	
≥20	2,576	8.53	3,442	6.14	
Level of deprivation					<0.001[b]
1 Least deprived	2,954	23.37	3,981	17.18	
2	3,091	24.46	4,996	21.56	
3	2,559	20.25	4,672	20.16	
4	2,390	18.91	5,360	23.13	
5 Most deprived	1,645	13.02	4,168	17.98	
Total with data	12,639	100.00	23,177	100.00	
Missing	17,571	58.16[c]	29,480	55.98[d]	

[a] To determine the association of each risk factor with diabetes status

[b] p value for trend

[c] % of 30,210

[d] % of 52,657

in crude (HR: 0.92; 95 % CI: 0.73–1.16) or multivariable-adjusted (HR: 1.02; 95 % CI: 0.79–1.30) models. Receiving no treatment was associated with an increased risk of breast cancer compared with sulfonylurea monotherapy (HR: 1.41; 95 % CI: 1.12–1.78). Combined sulfonylurea and metformin therapy was inversely associated with breast cancer risk (HR: 0.74; 95 % CI: 0.57–0.96). To allow direct comparisons of our results with those of authors who have used patients who received no pharmacological treatment as comparison group, we have provided Supplementary Table 1.

Controlling for HbA1c level among women who received insulin or oral hypoglycemic agents affected the point estimates for associations of insulin and combined sulfonylurea and metformin therapy with breast cancer, but did not alter inference. The results of the latency analyses

Table 2 Unadjusted and age-adjusted hazard ratios of the association of potentially confounding covariables with the risk of breast cancer

Variable	Unadjusted HR	95 % Confidence interval	Adjusted HR[a]	95 % Confidence interval
Age group at cohort entry				
<40	1.00			
40–49	2.71	(1.49–4.94)		
50–59	3.10	(1.72–5.57)		
60–69	3.10	(1.71–5.63)		
70 and above	3.48	(1.91–6.33)		
BMI				
Underweight (<18.5)	1.15	(0.70–1.91)	1.11	(0.67–1.85)
Normal (18.5–24.9)	1.00		1.00	
Overweight (25–30)	1.18	(0.98–1.42)	1.16	(0.96–1.39)
Obese (≥30)	1.47	(1.14–1.90)	1.45	(1.12–1.88)
Smoking status				
Never	1.00		1.00	
Past	1.13	(0.88–1.44)	1.08	(0.84–1.38)
Current	0.98	(0.77–1.26)	1.03	(0.80–1.32)
Drinking status				
Never	1.00		1.00	
Past	1.34	(0.64–2.82)	1.24	(0.59–2.61)
Current	1.18	(0.89–1.55)	1.20	(0.91–1.59)
Estrogen use				
None	1.00		1.00	
1–19	1.07	(0.87–1.32)	1.13	(0.91–1.42)
≥20	0.81	(0.66–1.00)	0.89	(0.71–1.11)
Level of deprivation				
1 Least deprived	1.00		1.00	
2	1.01	(0.80–1.28)	0.92	(0.73–1.16)
3	1.05	(0.82–1.34)	0.98	(0.76–1.25)
4	1.06	(0.83–1.35)	0.99	(0.77–1.27)
5 Most deprived	1.05	(0.72–1.53)	0.97	(0.67–1.42)
HbA1c[b]	0.90	(0.80–1.02)	0.93	(0.82–1.05)

HR Hazard ratio

[a] Adjusted for age, period, and region

[b] Represent only patients with prescribed treatment

(Supplementary Table 2) did not differ dramatically from the results presented in Table 5. The association with sulfonylurea and metformin was somewhat attenuated and consistent with chance, while the inverse association with "other" therapies was no longer present for the 3 year latency period analyses. The protective effect of metformin diminished with length of follow-up, while an imprecisely estimated increased risk was seen for long-term insulin use (Table 6).

Discussion

We found that women with diabetes were at a slightly higher risk of developing breast cancer than women without diabetes although the fully adjusted model was attenuated somewhat compared with the crude model, and our findings were consistent with chance. Nevertheless, the full-adjusted point estimate (HR = 1.12) is consistent with recent large meta-analyses (HR = 1.15 [1] and HR = 1.20 [2]), and a small real increased risk of breast cancer in women with diabetes cannot be ruled out. Although the effect estimates appeared to differ when associations of diabetes with pre- and postmenopausal breast cancers were examined separately, there was no statistical evidence of heterogeneity ($p = 0.79$), and we caution against overinterpretation of these stratified estimates. We observed an increased risk of all-cause mortality among women with breast cancer when comparing those with type 2 diabetes to those without. This illustrates the importance of continuing to adequately treat diabetes, and other comorbidities, in women with breast cancer. We were not able to control for stage, tumor grade, and morphology, but our results are consistent with existing literature [13, 19, 23].

There was only weak evidence of a protective effect of metformin on breast cancer risk, but this association was

Table 3 Adjusted hazard ratios of the association of diabetes with the risk of breast cancer

Diabetes status	Cases with breast cancer	Person-years of follow-up	Unadjusted HR	95 % Confidence interval	Adjusted HR[a]	95 % Confidence interval	Adjusted HR[b]	95 % Confidence interval	*p* value
Entire cohort									0.10
Without diabetes	714	255747.5	1.00		1.00		1.00		
With diabetes	873	594694.9	1.29	(1.16–1.44)	1.25	(1.12–1.40)	1.12	(0.98–1.29)	
Pre-menopausal breast cancer									0.99
Without diabetes	137	61513.6	1.00		1.00		1.00		
With diabetes	143	156579.2	0.61	(0.34–1.08)	1.08	(0.54–2.15)	1.01	(0.46–2.22)	
Postmenopausal breast cancer									0.09
Without diabetes	577	194233.9	1.00		1.00		1.00		
With diabetes	730	438115.7	1.31	(1.17–1.47)	1.25	(1.11–1.40)	1.13	(0.98–1.29)	

HR Hazard ratio

[a] Adjusted for age, period, and region

[b] Adjusted for age, period, region, and BMI

Table 4 Distribution of patients with diabetes by treatment received and breast cancer

Treatment pattern	Patients without breast cancer		Patients with breast cancer	
	Freq	%	Freq	%
None[a]	25,205	48.67	497	56.93
Insulin[b]	426	0.82	8	0.92
Sulfonylurea[c]	4,722	9.12	93	10.65
Metformin[d]	11,767	22.72	151	17.30
Sulfonylurea + metformin[e]	7,330	14.15	88	10.08
Sulfonylurea + metformin to insulin[f]	2,094	4.04	33	3.78
Other drugs and drug combinations	240	0.46	3	0.34

[a] No drugs prescribed

[b] Insulin initiated treatment

[c] Sulfonylurea only or sulfonylurea with drugs classified as other anti-diabetic drugs

[d] Metformin only or metformin with drugs classified as other anti-diabetic drugs

[e] Sulfonylurea and metformin, taken individually or at the same time

[f] Sulfonylurea and metformin, taken individually or in combination followed by insulin

attenuated markedly after controlling for covariables. While the risk estimates differ, our results are consistent with the recent paper by van Staa et al. [19], which performed a similar time-dependent analysis and a nationwide cohort study of the Danish population by Andersson [20]. The results are also consistent with earlier findings of Bodmer et al. (OR: 0.44; 95 % CI: 0.24–0.82) [15] and Libby et al. (HR: 0.63; 95 % CI: 0.53–0.75) [16] if the comparator group is changed to patients who did not receive any treatment. However, we caution against confounding by indication for these last comparisons.

Much of the variation in reported risk estimates between studies could be due to differences in the number of women, measurements used to determine diabetes status, definitions of treatment regimens, study design, and covariables taken into consideration in the analysis. Sample sizes of earlier studies ranged from a few hundred to 3.5 million (median = 6,800), but only 50 % of the studies reported more than 500 breast cancer cases. Diabetes assessments vary from patient self-reports to sophisticated laboratory measurements [2]. Adjustments for possible covariables likewise differ as some only considered age, while others also looked at lifestyle factors (smoking, drinking, and diet) and BMI [1, 2, 15, 16, 18, 38–41]. In spite of these, the results are fairly consistent, with similar results among those which adjusted for the same variables [2, 18, 41].

Compared with sulfonylurea use, the point estimates indicated a positive association between insulin and the risk of breast cancer, the risk appearing to increase with duration of diabetes, consistent with recent literature showing increased breast cancer risk with long-term use [41]. However, the confidence intervals in our study were very wide and the results consistent with no association. The reason why we observed a strong protective association of combined sulfonylurea and metformin use on breast cancer risk is unclear, but given the essentially null association of

Table 5 The association of diabetes treatment patterns with breast cancer

Treatment pattern	Cases with breast cancer	Person-years of follow-up	Unadjusted HR	95 % Confidence interval	Age-adjusted HR[a]	95 % Confidence interval	Adjusted HR[b]	95 % Confidence interval	Adjusted HR[c]	95 % Confidence interval
None	497	112139.7	1.35	(1.08–1.69)	1.43	(1.14–1.79)	1.41	(1.12–1.78)	–	–
Sulfonylurea	93	27308.2	1.00		1.00		1.00		1.00	
Insulin	8	2247.3	1.03	(0.49–2.17)	1.14	(0.54–2.39)	1.14	(0.54–2.39)	1.33	(0.63–2.83)
Metformin	151	48580.3	0.92	(0.73–1.16)	1.04	(0.81–1.32)	1.02	(0.79–1.30)	1.04	(0.79–1.37)
Sulfonylurea + metformin	88	34838.2	0.68	(0.52–0.88)	0.75	(0.57–0.98)	0.74	(0.57–0.96)	0.66	(0.50–0.88)
Sulfonylurea or metformin to insulin	33	8233.8	1.01	(0.68–1.50)	1.16	(0.79–1.72)	1.15	(0.77–1.71)	1.04	(0.68–1.59)
Other	3	1406.5	0.62	(0.20–1.93)	0.69	(0.22–2.16)	0.68	(0.22–2.13)	0.66	(0.21–2.07)

HR Hazard ratio

[a] Adjusted for age, period, and region

[b] Adjusted for age, period, region, BMI, and year of diagnosis

[c] Only included women who received treatment; adjusted for age, period, region, BMI, year of diagnosis, and weighted HbA1c

metformin versus sulfonylurea use with breast cancer, we suspect this an artifact.

In our analysis, we have taken into account changes in treatment regimens. By determining treatment patterns, we were able to elucidate the individual effects of the major drugs of interest (insulin, sulfonylurea, and metformin). We were able to control for severity by limiting this analysis to patients who were prescribed medication and by controlling for HbA1c levels although these produced broadly similar results as the analysis of all patients with diabetes.

We have also taken into account immortal time bias. Bias is introduced when an initial period where a patient does not have the exposure is misclassified in or excluded from the analysis and results in a spurious survival advantage for the exposure group. We have taken this into consideration by performing time-dependent analysis. Patients with diabetes have a period prior to their diabetes diagnosis during which they are unexposed and were classified as such. We have also appropriately allocated any initial treatment period in the treatment combination groups. For example, periods of initial sulfonylurea or metformin monotherapy prior to switching treatments were allocated to respective sulfonylurea or metformin therapy groups. A similar analysis has been done by van Staa et al. [19], but their results did not indicate long-term effects of treatment patterns or treatment combinations, nor did they consider latency time windows.

Our study is not without limitations and these should be considered in the interpretation of the results. First, the GPRD was not primarily created for research purposes. Data are independently collected by participating GP practices and reflect patient medical records. Information for other possible risk factors such as physical activity, diet, and waist–hip ratio were not available, and the analysis was limited to what was obtainable. Risk factor measurements and assessments were not standardized and differ within and between practices. However, as each practice in the GPRD is subject to quality control, the data are deemed of high research quality in terms of validity and accuracy. Also, matching by practice was performed to control for health provider–related factors.

In the cohort, there were only a small proportion of women in the treatment groups, and the small sample size resulted in lack of precision and low power. The same problem is encountered in the analysis stratified by whether the cancers were pre- or postmenopausal. Nevertheless, the estimates were within the range previously reported in other studies, despite not reaching conventional levels of statistical significance.

In conclusion, we found weak evidence that diabetes is associated with a small increased risk of breast cancer. Among treated women, there is no evidence that anti-

Table 6 The association of diabetes treatment regimen with breast cancer, by length of follow-up

Treatment pattern	Less than 1 year		1–5 years		>5 years	
	HR[a]	95 % Confidence interval	HR[a]	95 % Confidence interval	HR[a]	95 % Confidence interval
Sulfonylurea	1.00		1.00		1.00	
Insulin	1.01	(0.11–8.97)	0.54	(0.18–1.68)	2.25	(0.72–6.99)
Metformin	0.77	(0.35–1.73)	0.83	(0.55–1.24)	2.14	(1.00–4.57)

HR Hazard ratio

[a] Only included women who received treatment; adjusted for age, period, region, BMI, year of diagnosis, and weighted HbA1c

diabetes treatments modify the risk of developing breast cancer, with wide confidence intervals indicating imprecise effect estimates. Women with breast cancer and diabetes, however, had an increased all-cause mortality risk highlighting the potential importance of maintaining adequate glycemic control alongside anti-cancer treatments and subsequent follow-up.

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Conflict of interest The authors declare that they have to conflict of interest.

Ethical approval This study was approved by the Independent Scientific Advisory Committee (ISAC) of the MHRA. All observational studies performed using GPRD data are covered by the favorable ethical review of the Trent Multi-Centre Research Ethics Committee (05/MRE04/87).

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