

Is there an association between liraglutide use and female breast cancer in a real-world setting?

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Background: Liraglutide is a human glucagon-like peptide-1 receptor agonist approved for treatment of adults with type 2 diabetes mellitus at a maximum dose of 1.8 mg/day (Victoza[®]) and more recently at 3.0 mg/day for weight management (Saxenda[®]). During the evaluation of liraglutide for approval in weight management, a minor imbalance in the numbers of reported breast neoplasms was observed, motivating the present study. Our objective was to quantify the association between liraglutide and incidence of breast cancer (BC) among women in a real-world setting.

Patients and methods: Women initiating liraglutide or other antidiabetic therapies and who were enrolled in a large US health plan (2010–2014) were included. Comparisons of BC incidence rates were made between matched cohorts of initiators of liraglutide and cohorts of initiators of exenatide, metformin, pioglitazone, sulfonylureas, and dipeptidyl peptidase-4 inhibitors separately and as two “all comparators” groupings: with or without exenatide. Women with two or more claims with BC diagnosis codes within 61 days of each other were identified as possible cases, with additional confirmation by clinician review of comprehensive claims listings. Propensity score matched intention-to-treat (ITT) and time-on-drug (TOD) analyses were completed via Poisson regression. A latency analysis was performed.

Results: Relative risks for BC for liraglutide vs comparators from the ITT analyses ranged from 0.90 (95% CI: 0.67–1.22) for both the “all comparator” and “all comparator except exenatide” cohorts to 1.46 (95% CI: 0.96–2.22) relative to exenatide. Latency analyses excluding the first year of follow-up yielded slightly attenuated point estimates. The TOD analyses of cumulative use of liraglutide suggested no increased risk of BC.

Conclusion: Neither the ITT (overall or latency analysis) nor cumulative TOD analyses suggested an elevated risk of BC among liraglutide initiators. Short length of follow-up and the potential for confounding by unmeasured factors limit the full assessment of long-term risk.

Keywords: glucagon-like peptide-1 receptor agonist, type 2 diabetes, administrative claims, intention-to-treat, time-on-drug

Introduction

Liraglutide is a human glucagon-like peptide-1 receptor agonist (RA) approved for the treatment of adults with type 2 diabetes mellitus (T2DM) and more recently for weight management.^{1,2} In the randomized trials conducted for liraglutide 3.0 mg (Saxenda[®]; Novo Nordisk A/S, Copenhagen, Denmark) weight management indication, a twofold imbalance of breast neoplasms occurred. While the numbers were small, this imbalance

was not seen in the development program for T2DM.³ Most breast cancer (BC) cases were diagnosed during the first year of follow-up and occurred more frequently among women who lost more weight, potentially making discovery of the cancers more likely, suggesting detection bias.^{4,5} Nevertheless, these findings were sufficient to result in a concern that GLP-1 RAs might increase the risk of BC.⁶ Hicks et al have also presented a hypothesis relating to a possible biological effect.⁷ Preclinical studies have shown that GLP-1 receptors are located on normal breast tissue⁸ and suggest that GLP-1 analogs could promote tumor growth via fibroblast growth factor 7.^{9,10} Given that both T2DM and obesity are also known risk factors for BC, evaluation of medications that may increase the risk of BC is warranted.^{11–13} These concerns motivated the current investigation, taking advantage of an ongoing post-marketing safety study of liraglutide (1.2 mg and 1.8 mg) used for treatment of diabetes.

This study quantifies the relationship between liraglutide and BC relative to comparison groups using a new-user, active-comparator study design within a well-defined population of women from a US administrative health care database.¹⁴

Research design and methods

Study population and exposures

A prospective cohort study was conducted within the Optum Research Database, a large, geographically diverse population of commercial health insurance enrollees in the US. The study antidiabetic drugs (ADs) included liraglutide and comparator medications, including exenatide, metformin, pioglitazone, a sulfonylurea (SU; glyburide, glipizide, glimepiride), or a dipeptidyl peptidase-4 inhibitor (DPP-4i; sitagliptin, saxagliptin, linagliptin). Patients were women aged 18 years and over who initiated liraglutide or a comparator following at least 6 months of continuous health plan enrollment with complete medical and pharmacy benefits. Drug initiation was defined as an observed dispensing for a study AD, with the absence of a dispensing of that drug or drug class during the preceding baseline period of 6 months. Patients with any ICD ninth edition (ICD-9) diagnosis codes for malignant neoplasm of female breast (174.x) or personal history of malignant neoplasm of breast (V10.3) in the baseline period were excluded as prevalent cancers. This study was approved by the New England Institutional Review Board and Privacy Board.

Patients with eligible initiations were identified from 01 February 2010 to 30 November 2014. Due to changing

prescribing patterns and composition of drugs in the US market, cohorts were assembled quarterly for 2010–2012 and annually for 2013–2014 (14 calendar blocks). Follow-up time began the day after the first eligible initiation and continued until the earliest of disenrollment from the health plan, the occurrence of BC, or the end of the study period (December 31, 2014).

Covariates and propensity score (PS) modeling

PS matched analyses were conducted to balance baseline covariates characterizing demography, comorbidity, concomitant medications, and intensity of health care utilization. PSs were estimated separately for each of the seven comparison groups (five comparator drugs as well as for “all comparators” and “all comparators minus exenatide” [to remove any GLP-1 RA effect]).^{15–17} Key covariates, including use of other ADs including insulin, are noted in Table 1. Because PSs balance only measured covariates and their correlates, missing or miss-measured covariates may allow for residual confounding.¹⁸ Several hundred covariates were considered for the PS model to reduce the impact of potential residual confounding.¹⁹

Variables that were correlated with the exposures and likely to be correlated with BC were forced into the model to ensure that they contributed to the final PS estimates. Known risk factors for BC (eg, ductal carcinoma in situ, overweight/obesity), screening procedures, markers for diabetes severity, and variables representing baseline AD use were included. Additional predictors were selected with forward stepwise regression.

Within each of the 14 calendar blocks, initiators of liraglutide were PS matched 1:1 to initiators in each of the comparison groups.²⁰ Patients who did not match during one accrual time block but initiated that same drug or another study drug in a later accrual time block were again eligible for matching, and the PS was re-estimated using a 6-month baseline period prior to that initiation. Patients could enter into multiple matched cohorts but were allowed to match into each drug cohort pair only once. For logistical reasons, BC case status was determined prior to the PS estimation, but matching occurred without consideration of case status.

Outcome assessment

Potential claims-identified BC cases were initially identified by an algorithm developed by Setoguchi et al.²¹ The algorithm

required 2 or more days with claims with an ICD-9 code for malignant neoplasm of the breast (ICD-9 174.x) within 61 days of each other that were associated with inpatient, outpatient, or emergency room encounters. This algorithm had a high positive predictive value (PPV) within Medicare claims data (PPV 76.6%), but the population of the Optum study was younger and therefore was considered to be potentially at lower risk for BC.²² Given that the validity of measurement of outcomes will generally decrease with decreasing frequency of occurrence²³ and the Setoguchi study also included in situ BCs which were not included in this study, an additional review of detailed chronological listings of claims for services and treatments (patient profiles) for each potential case of BC was included. An independent clinical consultant conducted claims review using patient profiles covering the period 3 months prior to the qualifying BC diagnosis to the end of a woman's follow-up data or the end of the study (December 31, 2014). The clinical reviewer considered the presence and timing of relevant procedures (eg, biopsies and mammograms), diagnoses, treatments (eg, chemotherapy, radiation, mastectomy), types of specialists associated with diagnoses (eg, oncologist), and general patterns of care to classify potential cases into one of the following three categories:

1. New-onset (incident) BC (highly likely BC case occurring following study drug initiation date)
2. BC with onset date likely prior to study cohort entry date (prevalent case)
3. Not a case of BC (sufficient evidence to rule out BC)

For incident BC cases, the clinical reviewer also recorded the earliest date on which there was an indication that BC was present. Only incident cases were used in the analyses.

Statistical methods

Baseline characteristics are provided for liraglutide initiators and "all comparators" combined. Because of the complexity of drug use patterns, several methods were used to separately quantify risks associated with starting liraglutide, being on liraglutide currently, and cumulative exposure. As the primary analysis, an analog to intention-to-treat (ITT) analysis of randomized trials was applied to quantify the risk associated with starting treatment, attributing all follow-up time to the initial exposure cohort. Incidence rates (BC cases per 100,000 person-years) were estimated as the number of patients with BC divided by the person-years of follow-up. Poisson regression models were used to estimate incidence rate ratios (RRs) and 95% CIs for liraglutide vs

each comparator group. Generalized estimating equations (GEEs) were used to account for the paired nature of the data created by matching, except in cases when data were too sparse to support the GEE estimation.²⁴ In a latency analysis, person-time and BC cases from the first year of each patient's follow-up were excluded to focus on the probable period of any liraglutide effect on BC.

A time-on-drug (TOD) analysis was performed to evaluate the effect of recency of use of liraglutide. The dispensing date and days' supply (ie, a pharmacist-estimated number of days that a prescription is expected to last if taken according to the prescribing instructions) were used to categorize each person-day of follow-up into "current", "recent", and "past" use, for each study drug. "Current" use included the day after the dispensing date up through the end of the days' supply. A 31-day grace period was added to the end of days' supply to allow for variable adherence. "Current" use continued as long as new refill dispensings were observed before the grace period ended. Once the grace period expired, it was assumed the patient discontinued that drug. The next 31 days (person-time occurring between 32 and 62 days after "current" use) were considered as "recent" use. Person-time occurring after "recent" use was categorized as "past" use and persisted unless the patient re-started the same treatment, thereby re-entering the "current" use category. Because many patients switched and added AD therapies regularly, patients in matched pairs may have had use of both liraglutide and a comparator during follow-up. If BC was diagnosed while the patient was currently on liraglutide and had past use of the comparator, for example, the BC case and corresponding person-time were included in the incidence estimate for "current" liraglutide use and "past" comparator use. When patients had concurrent use of both drugs in the comparison, cases and person-time were included in "current" use for both drugs. Poisson regression was used to estimate the RRs and 95% CIs for "current", "recent", and "past" use of liraglutide vs the same "current-recent-past" category for comparators, adjusted by the logit of the PS to address confounding.

An additional TOD analysis quantified patients' cumulative time on liraglutide from cohort entry and compared the associated rate of BC within time unexposed to liraglutide (which was generally exposed to other ADs). For patients who initiated one of the other study drugs and later initiated liraglutide, cumulative exposure to liraglutide began at the time of that dispensing and subsequent person-time was no longer considered "liraglutide unexposed". RRs were estimated using Poisson regression modeling within categories of cumulative time (<6 months, 6–18 months, and >18 months)

relative to all “liraglutide unexposed” time, and models were adjusted for the logit of the PS.

The potential for surveillance bias was considered by comparing frequency of mammography during follow-up for each exposure group. The timing of BC diagnosis relative to cohort entry was examined for each of the seven matched cohorts. In addition, the distribution of cases by age group was examined, relative to the distribution of patients overall.

Results

Over the study period, 192,752 women were identified across all the drug cohorts. Of these, 4,202 (2.2%) had claims consistent with BC in the baseline period and were excluded from this analysis, leaving 188,550 women in the study.

There were 1,009 algorithm-identified cases, of which 151 (15.0%) were consistent with prevalent BC, eight (0.8%) were determined to be non-cases, and 850 (84.2%) were clinical reviewer-confirmed incident BC cases (Figure 1).

Among the matched liraglutide and “all comparator” initiators (n=17,880 in each cohort, Figure 1), there were 85 and 94 confirmed cases, respectively. Substantial differences in the sizes of matched cohort pairs were due to variations in available comparators across study drugs.

After PS matching, the baseline characteristics were well matched in the liraglutide and “all comparator” pairs (Table 1) and all other comparator pairs (data not shown). In the matched cohorts, the proportion of cases across age groups was similar, except that the liraglutide cohort cases tended to

Table 1 Baseline descriptive characteristics for all female initiators at the time of their first initiation and matched^a initiators (from all initiations)

Description	First initiation at cohort entry				All matched initiators (initial and subsequent initiations)			
	Liraglutide N=14,373		All comparators N=174,557		Liraglutide N=17,880		All comparators N=17,880	
	N	%	N	%	N	%	N	%
Demographic								
Age, years (median, IQR)	52	44.0–58.0	51	39.0–59.0	52	44.0–59.0	52	45.0–59.0
18–39	2,077	14.5	43,738	25.1	2,475	13.8	2,500	14.0
40–49	3,815	26.5	35,763	20.5	4,717	26.4	4,734	26.5
50–59	5,427	37.8	52,346	30.0	6,741	37.7	6,690	37.4
60–64	2,229	15.5	25,184	14.4	2,849	15.9	2,909	16.3
65+	825	5.7	17,526	10.0	1,098	6.1	1,047	5.9
Race (blacks)	2,087	14.5	27,928	16.0	2,665	14.9	2,606	14.6
Region								
Northeast	917	6.4	11,810	6.8	1,115	6.2	1,117	6.2
Midwest	3,119	21.7	45,572	26.1	3,969	22.2	4,014	22.4
South	8,673	60.3	91,235	52.3	10,693	59.8	10,636	59.5
West	1,664	11.6	25,940	14.9	2,103	11.8	2,113	11.8
Cohort entry (year)								
2010	3,867	26.9	56,093	32.1	4,010	22.4	4,010	22.4
2011	3,304	23.0	33,615	19.3	4,131	23.1	4,131	23.1
2012	2,911	20.3	30,992	17.8	3,936	22.0	3,936	22.0
2013	2,450	17.0	27,156	15.6	3,301	18.5	3,301	18.5
2014	1,841	12.8	26,701	15.3	2,502	14.0	2,502	14.0
Health care utilization								
Doctor cost (\$) (median, IQR)	756	343–1,763	623	266–1,546	762	349–1,767	785	359–1,840
Medication cost (\$) (median, IQR)	1,406	641–2,662	310	71–1,003	1,380	645–2,608	1,255	601–2,304
Total cost (\$) (median, IQR)	3,156	1,656–5,951	1,738	724–4,170	3,125	1,657–5,933	2,977	1,629–5,906
Number of 3-digit diagnosis codes								
0–5	2,581	18.0	40,541	23.2	3,145	17.6	3,098	17.3
6–8	3,028	21.1	39,112	22.4	3,775	21.1	3,928	22.0
9–13	4,199	29.2	48,438	27.7	5,232	29.3	5,181	29.0
14+	4,565	31.8	46,466	26.6	5,728	32.0	5,673	31.7
Number of unique drugs								
0–4	1,463	10.2	49,773	28.5	1,708	9.6	1,764	9.9

(Continued)

Table 1 (Continued)

Description	First initiation at cohort entry				All matched initiators (initial and subsequent initiations)			
	Liraglutide N=14,373		All comparators N=174,557		Liraglutide N=17,880		All comparators N=17,880	
	N	%	N	%	N	%	N	%
5–7	3,101	21.6	51,770	29.7	3,828	21.4	3,875	21.7
8–10	3,659	25.5	35,210	20.2	4,640	26.0	4,633	25.9
11+	6,150	42.8	37,804	21.7	7,704	43.1	7,608	42.6
Number of health care visits								
0–1	1,311	9.1	30,272	17.3	1,577	8.8	1,540	8.6
2–3	4,281	29.8	58,732	33.6	5,327	29.8	5,385	30.1
4–5	3,692	25.7	38,749	22.2	4,587	25.7	4,629	25.9
6+	5,089	35.4	46,804	26.8	6,389	35.7	6,326	35.4
Any emergency room visit	2,849	19.8	37,331	21.4	3,615	20.2	3,551	19.9
Any hospitalization	654	4.6	11,660	6.7	851	4.8	812	4.5
Lab tests (median, IQR)	9	4.0–15.0	7	3.0–13.0	9	4.0–15.0	9	5.0–15.0
Number of procedures (median, IQR)	1	0.0–3.0	1	0.0–2.0	1	0.0–3.0	1	0.0–3.0
Enrollment days (median, IQR)	514	332.0–852.0	489	305.0–868.0	607	369.0–996.5	651	374.0–1,038.0
Baseline diagnoses and procedures								
Type 1 diabetes	302	2.1	1,163	0.7	306	1.7	257	1.4
Type 2 diabetes	11,603	80.7	106,681	61.1	14,783	82.7	14,874	83.2
No diabetes diagnosis	2,468	17.2	66,710	38.2	2,791	15.6	2,749	15.4
Overweight	3,185	22.2	26,920	15.4	3,984	22.3	4,064	22.7
Any diabetes-related illness	1,690	11.8	9,757	5.6	2,108	11.8	2,179	12.2
Diabetes-related nephropathy	468	3.3	2,801	1.6	598	3.3	608	3.4
Diabetes-related neuropathy	1,016	7.1	5,471	3.1	1,252	7.0	1,314	7.3
Diabetes-related retinopathy	408	2.8	2,422	1.4	496	2.8	522	2.9
In situ breast carcinoma	9	0.1	73	0.0	10	0.1	10	0.1
Benign breast disease	294	2.0	3,473	2.0	349	2.0	367	2.1
Essential hypertension	8,427	58.6	82,230	47.1	10,660	59.6	10,698	59.8
Hyperlipidemia	8,799	61.2	77,828	44.6	11,033	61.7	11,068	61.9
Mammograms	3,112	21.7	32,226	18.5	3,892	21.8	3,883	21.7
Breast biopsy	11	0.1	110	0.1	14	0.1	13	0.1
Baseline health behaviors								
Smoking (positive)	385	2.7	5,806	3.3	479	2.7	551	3.1
Alcohol (positive)	24	0.2	441	0.3	27	0.2	37	0.2
Baseline drug dispensings								
Baseline tamoxifen (oral only) or aromatase inhibitors	29	0.2	700	0.4	35	0.2	42	0.2
Contraception/hormonal replacement	2,343	16.3	28,896	16.6	2,854	16.0	2,786	15.6
Insulin	3,755	26.1	14,361	8.2	4,387	24.5	4,321	24.2
Number of unique antidiabetic drugs								
0	4,763	33.1	125,192	71.7	5,248	29.4	5,274	29.5
1	5,309	36.9	36,074	20.7	6,809	38.1	6,879	38.5
2+	4,301	29.9	13,291	7.6	5,823	32.6	5,727	32.0

Notes: *Patients may have initiated multiple times during the study period, but are allowed to match only once into each drug cohort pair.

have a higher proportion in the 60–64 years group and a lower proportion in 40–49 years (Table S1). For all cohorts, the distribution of cases was skewed toward the older ages, relative to the distribution of patients by age. For example, while 5.9% of the “all comparator” patients were age 65+ years, 11.7% of the

cases were in that age group. A similar pattern was observed in the liraglutide cohort (6.1% of liraglutide patients were age 65+ years vs 10.6% of cases). Median lengths of follow-up were similar “within” matched drug cohorts, with some variation “across” matched sets (Table 2). Results for the ITT

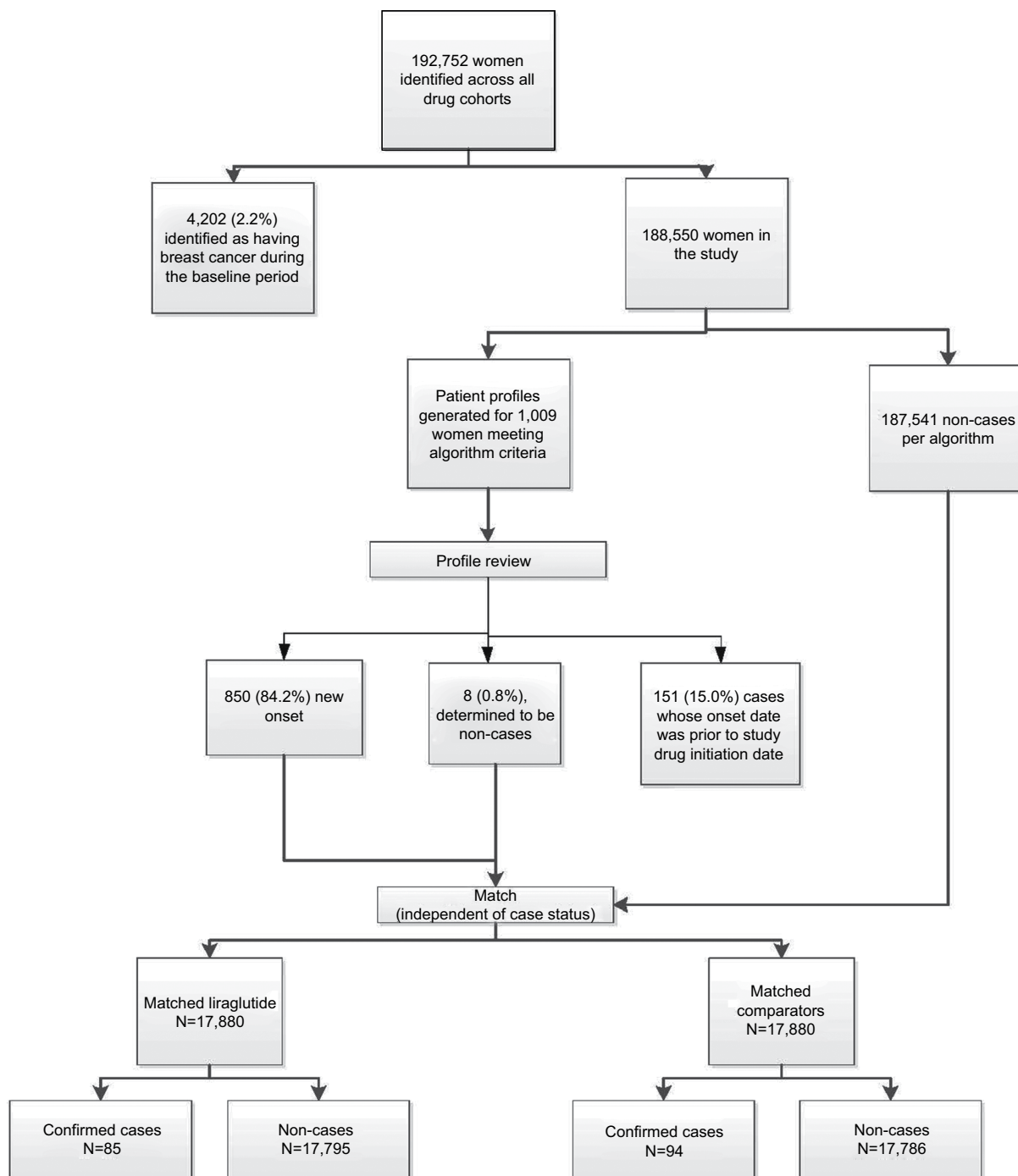


Figure 1 Identification process and outcome for breast cancer case adjudication

Notes: Numbers in the upper portion of this figure reflect the number of actual women and numbers in the matched section of the figure reflect number of matched initiations, including some women who initiated multiple times.

Table 2 Study follow-up time^a in days for matched^b liraglutide/study drug pairs

Study drug	Matched pairs (first and subsequent initiations)				
	N	Comparator		Liraglutide	
		Median	IQR	Median	IQR
All comparators	17,880	526	237–954	527	234–956
All comparators (excluding exenatide)	17,729	531	242–954	527	233–956
Exenatide	9,557	574	256–987	566	251–979
DPP-4i (saxagliptin, sitagliptin, linagliptin)	12,173	531	231–942	520	233–939
Metformin	11,934	515	238–931	497	220–911
Glyburide/glipizide/ glimepiride	12,418	496	222–870	493	221–897
Pioglitazone	8,009	606	261–1,112	611	264–1,120

Notes: ^aFollow-up begins on the day following initiation and continues until end of enrollment, or end of study period (December 31, 2014), whichever comes first. ^bPatients may have initiated multiple times during the study period, but are allowed to match only once into each drug cohort pair.

Abbreviation: DPP-4i, dipeptidyl peptidase-4 inhibitor.

and TOD analyses are presented in Figure 2. In the primary analysis (ITT), RRs ranged from a low of 0.90 for both the comparison with “all comparators” (95% CI: 0.67–1.21) and “all comparators excluding exenatide” (95% CI: 0.67–1.22) to a high of 1.46 (95% CI: 0.96–2.22) relative to exenatide.

Approximately 50% of all BC cases in the matched cohorts occurred during the first year of follow-up, leading to less precise estimates in the latency analysis. The observed RRs ranged from a low of 0.83 (95% CI: 0.55–1.26) for “all comparators excluding exenatide” to a high of 1.50 (95% CI: 0.87–2.58) for metformin. The RRs in the latency analyses were all the same or smaller and less precise, with the exception of the increase observed for the metformin comparison, from RR 1.10 (95% CI: 0.76–1.61) to 1.50 (95% CI: 0.87–2.58).

In the TOD analyses, RRs during “current” use ranged from a low of 0.95 (95% CI: 0.64–1.40) for SUs to a high of 1.63 (95% CI: 0.92–2.88) for pioglitazone. RRs for “recent” use (32–62 days after current use) were consistently lower than “current” use. RRs for “past” time followed no consistent pattern. The cumulative TOD analysis was performed only for the liraglutide vs “all comparator” matched cohorts. RRs were 0.79 (95% CI: 0.55–1.13) for <6 months of liraglutide exposure, 1.03 (95% CI: 0.69–1.54) for 6–18 months of exposure, and 0.98 (95% CI: 0.55–1.76) for ≥18 months of exposure. Across all ITT and TOD analyses, all comparisons had 95% CIs that included the null.

Assessment of surveillance bias revealed that liraglutide and exenatide cohorts had more mammograms during follow-up than the other cohorts (mean of 0.78 [SD 1.15] and 0.84 [SD 1.22], respectively). In contrast, the SU cohort had a mean of 0.51 (SD 0.95). Within each matched cohort,

the time to diagnosis was similar with the exception of the metformin cohort which had a substantially shorter median time to diagnosis (309 vs 415 days) and the DPP-4i cohort which had a longer median time (479 vs 339 days) (Table 3; also see Figures S1–S7).

Discussion

Overall, these data are consistent with no association between the use of liraglutide and risk of incident BC across different comparators and several different analyses, similar to the findings of Hicks et al and the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial.^{7,25} Baseline differences between liraglutide initiators and those of other ADs were largely accounted for with the PS matching.

The motivation for this study was the observation of an imbalance in the reported proportion of BC cases in the early liraglutide weight management trials in which adjudicated BCs were reported in 17 (0.7%) of 2,379 liraglutide-treated women compared with three (0.2%) of 1,300 placebo-treated women.³ Most cases were diagnosed during the first year of follow-up, which would likely include BCs that were preclinical at the time of study initiation; follow-up in general was limited (mean of 46 weeks, maximum of 160 weeks). The numbers included ductal carcinoma in situ (four liraglutide and one placebo).

A recently published observational study in the UK using the Clinical Practice Research Datalink compared BC incidence in initiators of GLP-1 RAs (exenatide, liraglutide, others) with initiators of DPP-4i.⁷ No overall increased risk of BC associated with use of GLP-1 RAs was found (adjusted hazard ratio [HR] 1.40 (95% CI: 0.91–2.16). Findings were

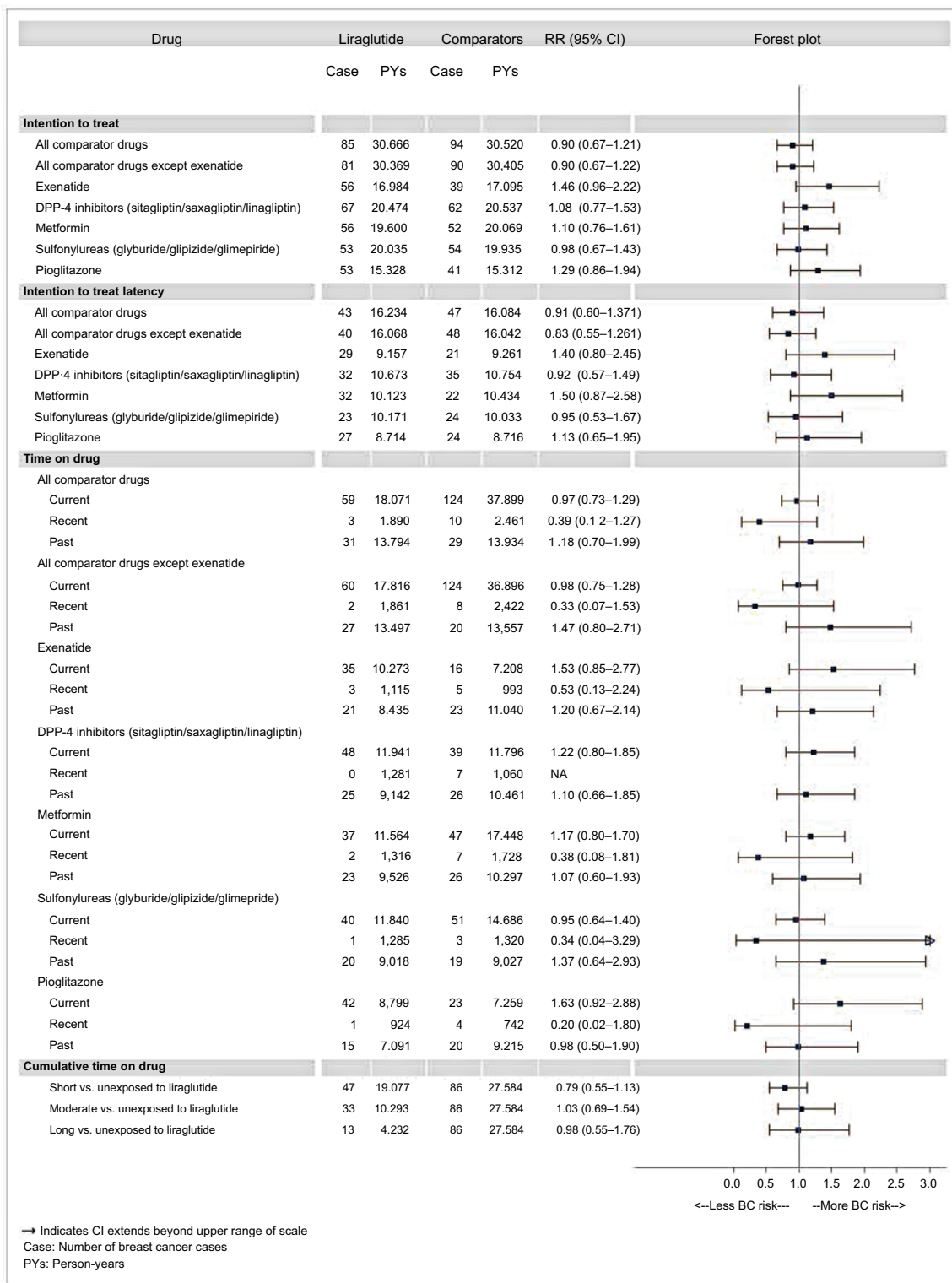


Figure 2 Propensity score matched ITT and TOD analyses for BC.
Abbreviations: ITT, intention-to-treat; TOD, time-on-drug; RR, rate ratio; BC, breast cancer.

similar when liraglutide was the only GLP-1 RA compared to DPP-4i. While the study included 44,984 patients, the primary analysis involved only 498 patients using a GLP-1 RA and 2,422 patients using a DPP-4i. These findings were

consistent with findings in the recently completed LEADER trial, comparing liraglutide with placebo. Patients were followed for up to 172 weeks (median, 86 weeks). In LEADER, a small number of malignant breast neoplasms were identified

Table 3 Time^a to BC diagnosis in days for adjudicated BC cases (all first initiations and matched^b liraglutide/study drug pairs)

Study drug	First initiation at cohort entry			Matched pairs (first and subsequent initiations)					
	Case N	Median	IQR	Comparators			Liraglutide		
	Case N	Median	IQR	Case N	Median	IQR	Case N	Median	IQR
Unmatched									
Liraglutide and comparators	797	395	162–718						
Liraglutide	76	382	181–641						
Matched cohorts									
All comparators	721	395	161–735	94	361	148–775	85	391	183–667
All comparators excluding exenatide	691	395	159–749	90	396	158–714	81	362	183–628
Exenatide	30	397	192–552	39	412	205–676	56	394	186–710
DPP-4i (saxagliptin, sitagliptin, linagliptin)	110	450	139–762	62	479	172–795	67	339	174–598
Metformin	388	405	182–750	52	309	159–639	56	415	168–657
Sulfonylureas (glyburide/glipizide/glimepiride)	134	366	131–669	54	321	111–586	53	332	186–480
Pioglitazone	59	395	162–708	41	421	219–689	53	391	175–598

Notes: ^aTime is from day after index date to BC adjudication-determined diagnosis date. ^bPatients may have initiated multiple times during the study period, but are allowed to match only once into each drug cohort pair.

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; BC, breast cancer.

in both groups: 21 patients in the liraglutide group (1.3%, 0.33/100 person-years) and 20 patients in the placebo group (1.2%, 0.31/100 person-years, HR 1.06; 95% CI: 0.57–1.96).²⁵

Several limitations should be considered when interpreting our study findings. Despite balance on a wide array of measurable baseline covariates, the potential for residual confounding by unmeasured factors remains. In particular, a patient's body mass may influence physicians' prescribing, particularly for antidiabetic medications which are known to be associated with additional weight loss benefits (eg, liraglutide). If body mass is sufficiently correlated with the included measured covariates, then residual confounding is unlikely, but this is not testable with the available data.

A substantial proportion of the BC cases in the current study were observed within the first year following study drug initiation, and many within the first 6 months. It is recognized that causative agents do not lead to cancers immediately after exposure and may manifest clinically only after several decades.²⁶ While it is possible that diabetic therapies might accelerate the development of a cancer already initiated, each of the pathways to clinically evident cancer requires time before the cancer reaches the point of detection.²⁷

A latency analysis addressed the concern about inclusion of prevalent but undiagnosed cancers at the time of drug initiation. In general, both the overall and the latency analyses provided similar results. Less than a quarter of the matched initiators had 3 or more years of follow-up. Both

the current study and the clinical trials had follow-up times that may not allow for full assessment of long-term effects, given the biologically plausible development times for BC.²⁸

The complexity of therapies for patients with diabetes in real-world use settings poses challenges to the design and interpretation of a matched cohort study for BC. The definition of "initiation" required only 6 months with no use of that drug and consequently earlier exposures may not have been captured. In addition to the comparator medications included in this study, patients receive additional ADs and therapies for comorbidities, such as obesity and hypertension. In fact, nearly half of all initiators in each drug cohort had baseline dispensings for metformin (other than metformin initiator cohort). As their diabetes progresses, patients may switch, drop, or add drugs to the initial regimen. Despite the inclusion of many baseline covariates in the PSs to balance the cohorts with respect to these exposures, including insulin and the number of antidiabetic agents, use may differ during the follow-up period leading up to the BC diagnosis.

The first TOD analysis allocated person-time into "current", "recent", and "past" time. While for an acute outcome such as a hypersensitivity reaction, the expectation is that "current" time on the drug would be most critical, for outcomes such as cancer with long latency periods, "past" use is highly relevant, but requires lengthy follow-up. The second type of TOD analysis evaluated the potential for a dose–response relationship through calculation of cumulative exposure to liraglutide. In the present study, the similarity

of conclusions for the ITT and TOD approaches lends more weight to the finding of no excess risk for BC among liraglutide initiators.

Both obesity and diabetes are recognized risk factors for BC; however, since all of the patients in the study are on antidiabetic medications, and cohorts were matched on many factors related to obesity, the effect estimates are likely to be unconfounded by these factors.

There are a number of strengths. The cohorts were enumerated via a large administrative claims database. The size and breadth of this database enabled numerous comparator cohorts to which liraglutide could be compared, representing therapies with different mechanisms of action. The cohorts were matched across a wide range of variables, including known risk factors for BC. A validated algorithm was used to identify BC cases, supplemented with claims profiles review to further validate case status. This review process is less resource intensive than medical chart adjudication, allowing for the review of a larger population of patients, and since the review is blinded, clinical interpretation of case status was independent of exposure. Analyses to other plausible sources of bias were performed.

Conclusion

Although the relatively short length of follow-up and the potential for residual confounding by unmeasured factors such as obesity limit the ability to fully assess long-term risk, overall the data appear consistent with no effect of liraglutide on the occurrence of BC.

Acknowledgments

The authors would like to acknowledge the contributions of Nicole Brooks for her project oversight and Danielle Cupka for her technical assistance in preparing this manuscript.

This study was funded by a research contract with Novo Nordisk A/S. As part of this contract, Optum Epidemiology retains the right to publish all results. Because this work was undertaken to meet a regulatory requirement, Novo Nordisk reviewed and commented on the protocol and statistical analysis plan underlying this work as well as the final report. The original study design and analytic plan required US FDA approval.

Author contributions

DDD had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Because this work was in response to a regulatory (European Medicines Agency) request, Novo Nor-

disk reviewed and commented on the protocol and statistical analysis plan underlying this work. Study concept and design: DDD, DF, and KM; acquisition of data: LL and HN; analysis and interpretation of data: DDD, DF, KM, LL, and HN; drafting of the manuscript: DF; and critical revision of the manuscript for important intellectual content: DDD, KM, AM-P, AHO, and MSK. All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

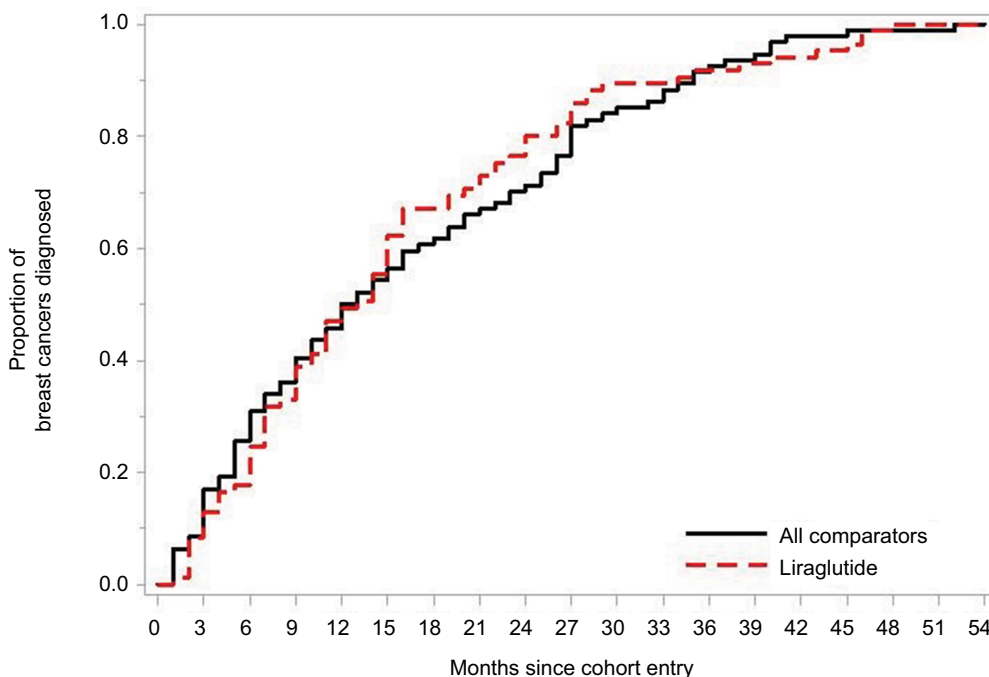
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Supplementary materials

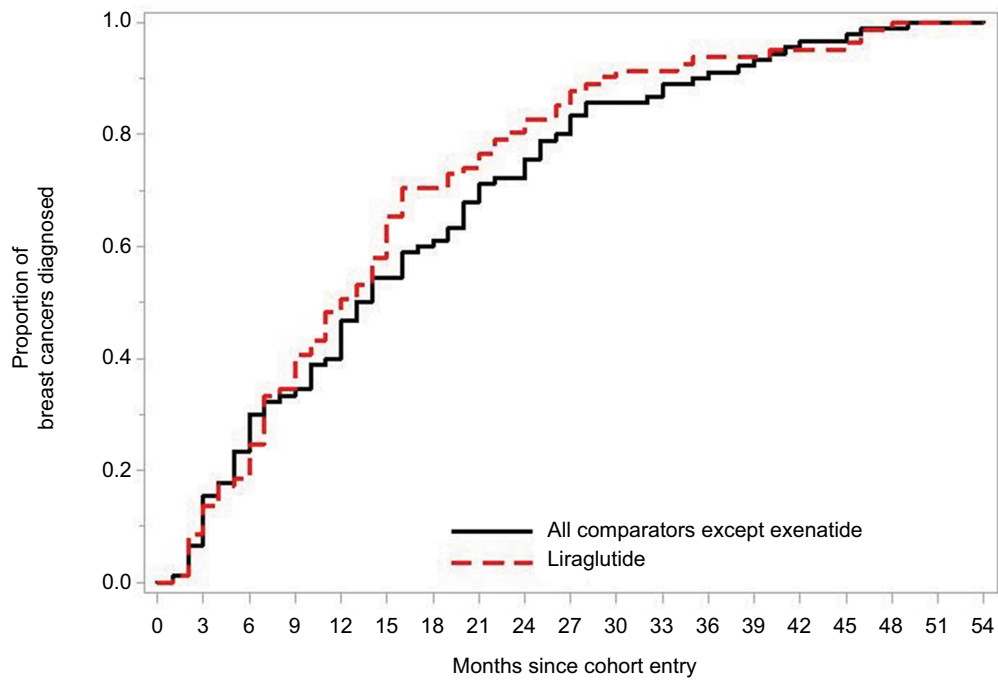
Table S1 Distribution of breast cancer cases and patients by age group and matched cohorts

Age group	All comparator cohort					Liraglutide cohort				
	18–39 (%)	40–49 (%)	50–59 (%)	60–64 (%)	65+ (%)	18–39 (%)	40–49 (%)	50–59 (%)	60–64 (%)	65+ (%)
Cases	4.3	25.5	43.6	14.9	11.7	1.2	16.5	42.4	29.4	10.6
Patients	14.0	26.5	37.4	16.3	5.9	13.8	26.4	37.7	15.9	6.1



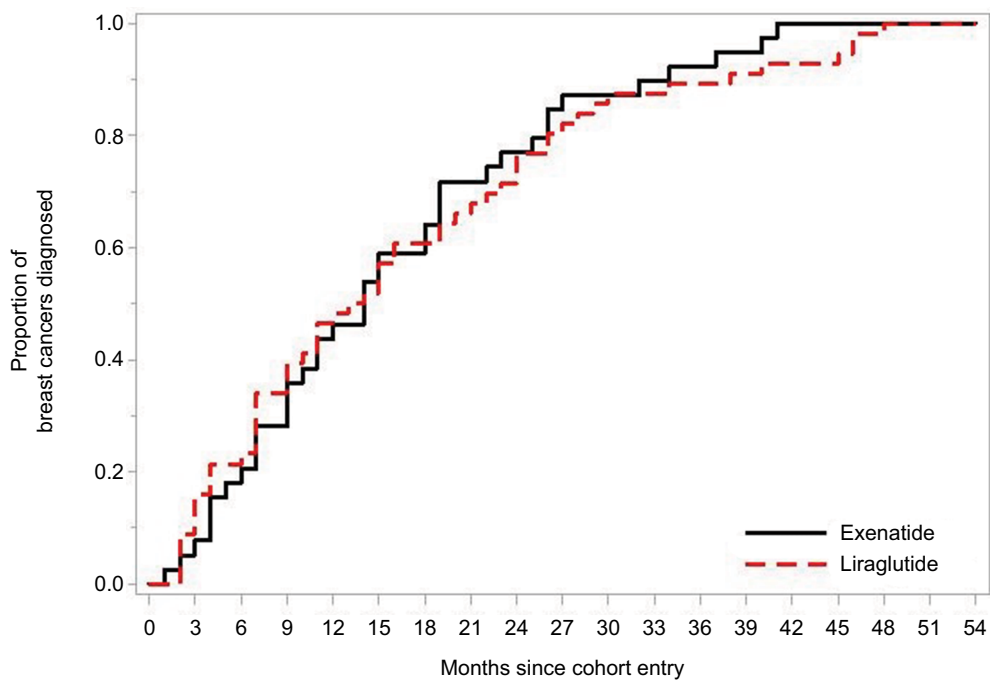
# diagnosed	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Comparator	0	16	29	38	47	53	58	63	67	77	80	83	87	89	92	93	93	93	94
Liraglutide	0	11	21	33	42	53	57	62	68	73	76	76	78	79	80	82	85	85	85

Figure S1 Time to diagnosis: liraglutide and all comparators.



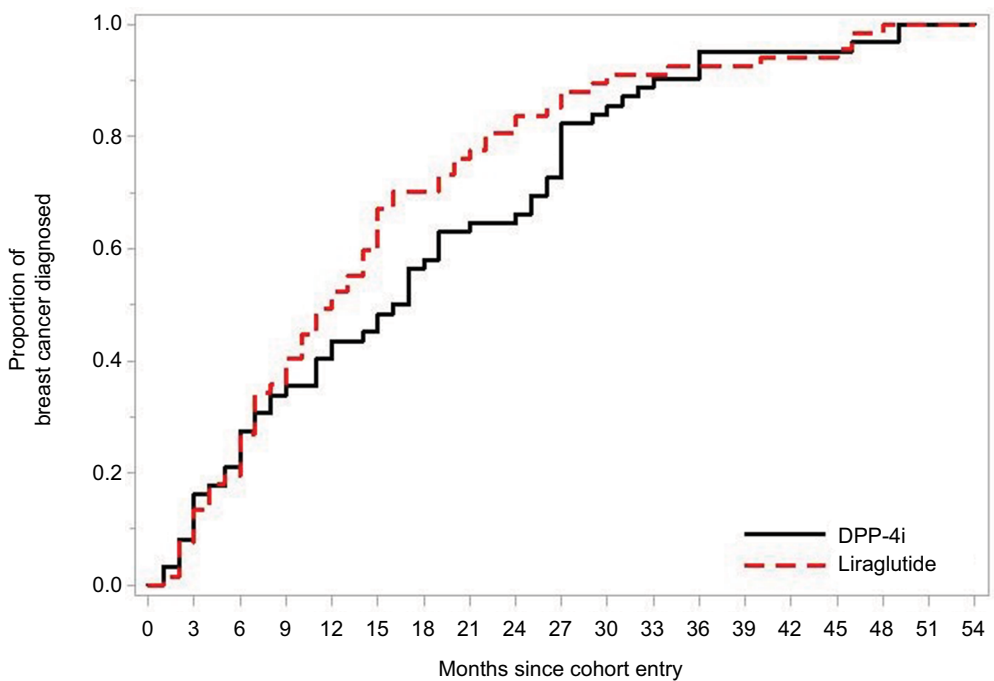
# diagnosed	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Comparator	0	16	27	31	42	49	55	64	68	75	77	80	82	84	87	88	89	90	90
Liraglutide	0	11	20	33	41	53	57	62	67	71	74	74	76	76	77	78	81	81	81

Figure S2 Time to diagnosis: liraglutide and all comparators excluding exenatide.



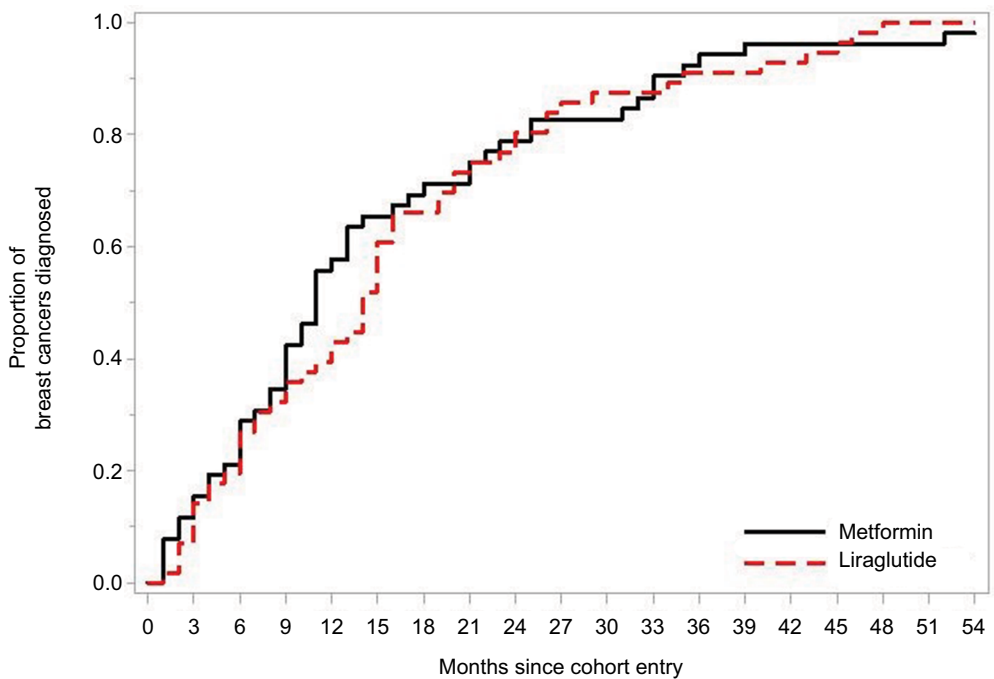
# diagnosed	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Comparator	0	3	8	14	18	23	25	28	30	34	34	35	36	37	39	39	39	39	39
Liraglutide	0	9	13	22	27	32	34	38	43	46	49	49	50	51	52	53	56	56	56

Figure S3 Time to diagnosis: liraglutide and exenatide.



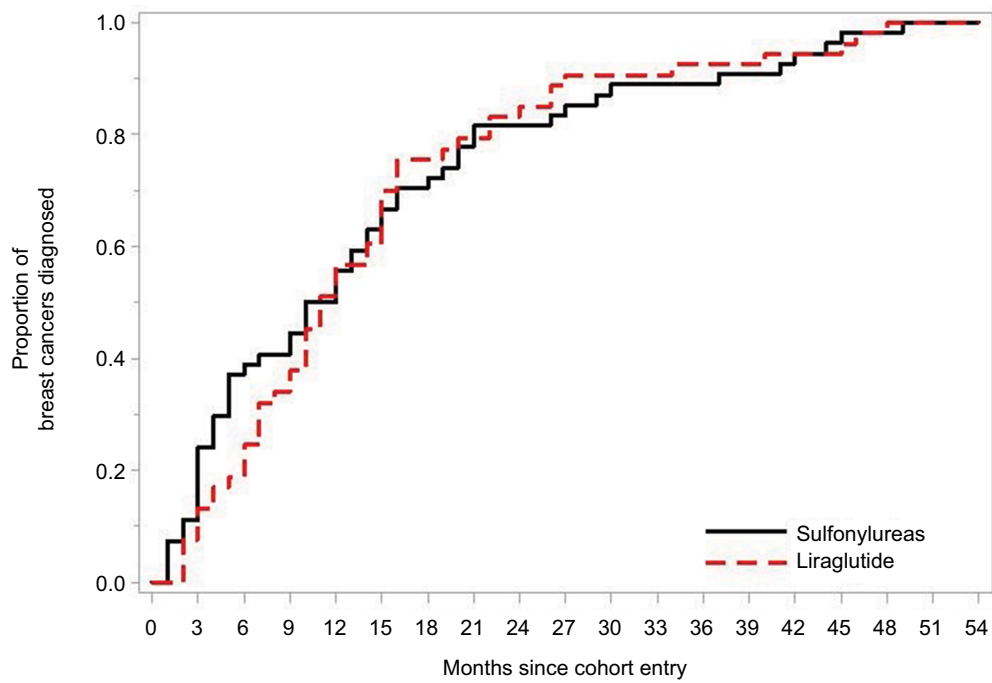
# diagnosed																			
Comparator	0	10	17	22	27	30	36	40	41	51	53	56	59	59	59	59	60	62	62
Liraglutide	0	9	18	27	35	45	47	52	56	59	61	61	62	62	63	64	67	67	67

Figure S4 Time to diagnosis: liraglutide and DPP4i.
Abbreviation: DPP4i, dipeptidyl peptidase-4 inhibitor.



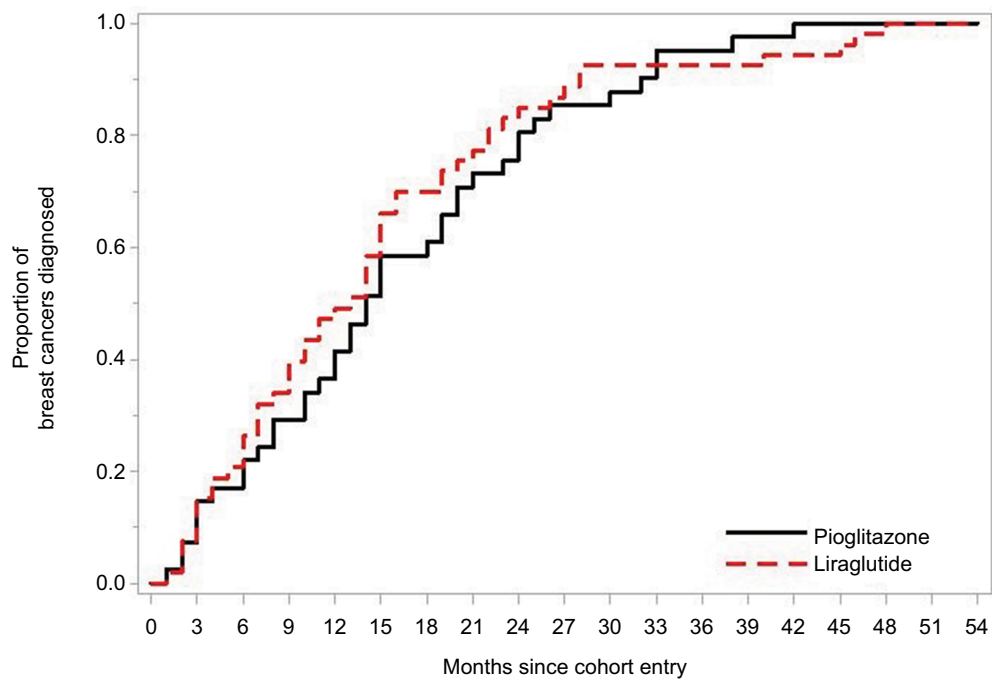
# diagnosed																			
Comparator	0	8	15	22	30	34	37	39	41	43	43	47	49	50	50	50	50	50	51
Liraglutide	0	8	15	20	24	34	37	42	45	48	49	49	51	51	52	54	56	56	56

Figure S5 Time to diagnosis: liraglutide and metformin.



# diagnosed	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Comparator	0	13	21	24	30	36	39	44	44	46	48	48	48	49	51	53	53	54	54
Liraglutide	0	7	13	20	30	37	40	42	45	48	48	48	49	49	50	51	53	53	53

Figure S6 Time to diagnosis: liraglutide and sulfonyleureas.



# diagnosed	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Comparator	0	6	9	12	17	24	25	30	33	35	36	39	39	40	41	41	41	41	41
Liraglutide	0	8	14	21	26	35	37	41	45	47	49	49	49	49	50	51	53	53	53

Figure S7 Time to diagnosis: liraglutide and pioglitazone.

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