Glucagon-like peptide-1 analogues and risk of breast cancer in women with type 2 diabetes: population based cohort study using the UK Clinical Practice Research Datalink

Blánaid M Hicks,[1,2] Hui Yin,[1] Oriana H Y Yu,[1,3] Michael N Pollak,[4,5] Robert W Platt,[1,2,6,7] Laurent Azoulay[1,2,4]

[1]Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, 3755 Côte Sainte-Catherine, H-425.1, Montréal H3T 1E2, Canada

[2]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montréal

[3]Division of Endocrinology, Jewish General Hospital

[4]Gerald Bronfman Department of Oncology, McGill University

[5]Segal Cancer Center, Lady Davis Institute for Medical Research, Jewish General Hospital

[6]Department of Pediatrics, McGill University

[7]Research Institute of the McGill University Health Centre, Montreal

Correspondence to: L Azoulay laurent.azoulay@mcgill.ca

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2016;355:i5340 http://dx.doi.org/10.1136/bmj.i5340

Accepted: 23 September 2016

ABSTRACT

OBJECTIVE

To determine whether the use of glucagon-like peptide-1 (GLP-1) analogues, compared with the use of dipeptidylpeptidase-4 (DPP-4) inhibitors, is associated with an increased risk of incident breast cancer in patients with type 2 diabetes.

DESIGN

Population based cohort study.

SETTING

Clinical Practice Research Datalink, UK.

PARTICIPANTS

44 984 women aged at least 40 years, who were newly treated with glucose lowering drugs between 1 January 2007 and 31 March 2015, with follow-up until 31 March 2016.

MAIN OUTCOMES AND MEASURES

Time varying use of GLP-1 analogues compared with use of DPP-4 inhibitors, with exposures lagged by one year for latency purposes. Time dependent Cox proportional hazards models were used to estimate adjusted hazard ratios with 95% confidence intervals of incident breast cancer associated with use of GLP-1 analogues overall, by cumulative duration of use, and time since initiation.

RESULTS

The cohort was followed for a mean of 3.5 years (standard deviation 2.2), with 549 incident events of breast cancer recorded (crude incidence 3.5 (95% confidence interval 3.3 to 3.8) per 1000 person years). Overall, compared with use of DPP-4 inhibitors, use of GLP-1 analogues was not associated with an increased risk of breast cancer (incidence 4.4 *v* 3.4 per 1000 person years; hazard ratio 1.40 (95% confidence interval 0.91 to 2.16)). Hazard ratios gradually increased with longer durations of use, with a peak between two to three years of GLP-1 use (2.66 (95% confidence interval 1.32 to 5.38)), and returned closer to the null after more than three years of use (0.98 (0.24 to 4.03)). A similar pattern was observed with time since initiation of GLP-1 analogues.

CONCLUSIONS

In this population based cohort study, use of GLP-1 analogues was not associated with an overall increased risk of breast cancer. Although it is not possible to rule out a tumour promoter effect, the observed duration-response associations are likely the result of a transient increase in detection of breast cancers in GLP-1 analogue users.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Early randomised controlled trials of liraglutide, a glucagon-like peptide-1 (GLP-1) analogue, have reported imbalances in breast cancer events compared with placebo

Despite calls from regulatory agencies for further investigation, no observational studies have been conducted so far to analyse this safety concern

WHAT THIS STUDY ADDS

Use of GLP-1 analogues was not associated with an overall increased risk of breast cancer

Associations were observed with of GLP-1 analogue use, at two to three years and three to four years after initiation of treatment; however, these associations returned closer to the null with longer durations of treatment

Although it is not possible to rule out a tumour promoter effect, the observed duration-response associations are likely the result of a transient increase in detection of breast cancers in GLP-1 analogue users

Introduction

Glucagon-like peptide-1 (GLP-1) analogues and dipeptidylpeptidase-4 (DPP-4) inhibitors are incretin based drugs used as second or third line treatments for type 2 diabetes. Although these drugs have been associated with favourable effects on hypoglycaemia and body weight,[1] there have been concerns that their use could increase the risk of certain neoplasms, such as pancreatic cancer.[2 3] There are also emerging concerns by regulatory agencies—including the US Food and Drug Administration and the European Medicines Agency—that GLP-1 analogues, in particular, might increase the risk of breast cancer.[4 5]

In randomised controlled trials of weight management, there were imbalances in the number of breast cancer events among patients randomised to the GLP-1 analogue liraglutide versus placebo (15 *v* 3 events; incidence 4.36 *v* 1.80 per 1000 person years).[5 6] A similar pattern was also observed in trials of patients with type 2 diabetes (9 *v* 1; 2.97 *v* 1.17 per 1000 person years).[5] However, these findings are at odds with those of the recently published LEADER trial (liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results).[7] In the LEADER trial, which randomised 9340 patients followed for a median of 3.8 years, researchers found no imbalances in breast cancer events among those randomised to liraglutide versus placebo (21/1657 (1.3%) *v* 20/1680 (1.2%)).[7]

One hypothesis for the observed imbalance in the aforementioned randomised controlled trials relates to weight loss induced by GLP-1 analogues, possibly leading to a better detection of breast masses and

increased uptake and accuracy of mammography.[5 6] Indeed, the discrepancy between earlier trials and the recent LEADER trial might be due to a transient increase in detection of breast cancers relatively soon after treatment initiation. However, a competing hypothesis relates to a possible biological effect. Preclinical studies have shown that GLP-1 receptors are located on normal breast tissue[8] and suggest that GLP-1 analogues could promote tumour growth via fibroblast growth factor 7 (FGF7).[9 10]

To our knowledge, no observational studies have been conducted to assess this important safety concern. Thus, this population based study aimed to assess whether the use of GLP-1 analogues to treat type 2 diabetes is associated with an increased risk of breast cancer.

Methods

Data source

This study was conducted by use of the UK Clinical Practice Research Datalink (CPRD). The CPRD includes data from about 700 general practices comprising over 14 million patients; this database has been shown to be representative of the UK population.[11] The CPRD records demographic information, anthropometric data, lifestyle information, medical diagnoses and procedures, and prescription data that have been shown to be valid and of high quality.[12 13] Furthermore, breast cancer diagnoses recorded in the CPRD have been shown to be highly concordant (>90%) with those recorded in the UK National Cancer Data Repository.[14]

The study protocol was approved by the independent scientific advisory committee of the CPRD (protocol number 16_096R) and by the research ethics board of the Jewish General Hospital, Montreal, Canada.

Study population

We identified all female patients, at least 40 years of age, who were newly prescribed a non-insulin glucose lowering drug (including metformin, sulfonylureas, prandial glucose regulators, thiazolidinediones, acarbose, DPP-4 inhibitors, GLP-1 analogues, and sodium-glucose cotransporter-2 inhibitors) between 1 January 1988 and 31 March 2015. Patients were required to have at least one year of medical history in the CPRD before their first prescription. We excluded those patients prescribed insulin at any time before their first prescription for a non-insulin glucose lowering drug, because this earlier prescription likely represented those individuals with advanced disease. Finally, we excluded female patients previously diagnosed with gestational diabetes or polycystic ovarian syndrome, because these are other indications for metformin.

Using the base cohort, we identified all patients who initiated a new glucose lowering drug class on or after 1 January 2007 (the year that the first incretin based drugs (sitagliptin and exenatide) entered the UK market) until 31 March 2015. These patients included those with a first ever diabetes drug prescription as well as those who added on or switched to a glucose lowering drug class not previously used in their treatment history. Cohort entry was defined by the date of this first prescription. Patients with a previous diagnosis of breast cancer (malignant and in situ) at any time before cohort entry were excluded. We also excluded patients with less than one year follow-up after cohort entry for latency purposes and to minimise detection bias due to increased contact with healthcare professionals at drug initiation. Consequently, patients diagnosed with breast cancer in the first year after cohort entry were not included in the cohort.

All patients meeting the study inclusion criteria were followed starting one year after cohort entry and until a first ever diagnosis of breast cancer (malignant and in situ, identified on the basis of Read codes; available on request), death from any cause, end of registration with the general practice, or the end of the study period (March 31, 2016), whichever occurred first.

Exposure assessment

We used a time dependent exposure definition. The exposure groups were defined hierarchically, with each person day classified into one of three mutually exclusive categories: GLP-1 analogues (exenatide, liraglutide and lixisenatide, alone or in combination with other glucose lowering drugs), DPP-4 inhibitors (sitagliptin, vildagliptin, and saxagliptin, alone or in combination with other glucose lowering drugs), and other glucose lowering drugs. All exposures were lagged by one year to account for a minimum latency period and to minimise reverse causality. Thus, patients initiating a glucose lowering drug were considered unexposed until one year after the date of the first prescription and considered exposed thereafter. The reference category was use of DPP-4 inhibitors, because these compounds are also incretin based drugs but have not been associated with breast cancer incidence in previous large randomised controlled trials.[15-18] Furthermore, the first GLP-1 analogue and DPP-4 inhibitor were introduced in the UK in the same year (2007), and both drug classes are recommended as second to third line treatments,[19] thereby minimising potential confounding by indication.

Based on the above exposure definition, we also defined the use of GLP-1 analogues in terms of cumulative duration of use and time since initiation. Cumulative duration of use was defined, in a time dependent fashion, as the total number of years of use calculated by summing the durations associated with each prescription between cohort entry and the risk set date (that is, time of the event). Time since initiation was defined, in a time dependent fashion, as the time between the first GLP-1 analogue prescription and the risk set date.

Potential confounders

All models were adjusted for the following variables measured at cohort entry: year of cohort entry, age, body mass index (<25, 25-29, ≥30), smoking status (current, former, never, unknown), alcohol related disorders (including alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis, and hepatic flexure), haemoglobin A1c (most recent laboratory result before

cohort entry), and duration of treated diabetes (defined as the time between first non-insulin prescription and cohort entry).

The models were also adjusted for the presence of microvascular complications of diabetes (neuropathy, renal disease, retinopathy, and peripheral arteriopathy; measured at any time before cohort entry), and the number of unique glucose lowering drugs received in the year before cohort entry, both as proxies for diabetes severity. Additionally, we adjusted for previous oophorectomy, previous cancer diagnosis (excluding non-melanoma skin cancer), and the total number of unique non-glucose lowering drugs prescribed in the year before cohort entry (as a general measure of comorbidity[20]). Finally, all models were adjusted for the use of statins, hormonal replacement therapy, and oral contraceptives, measured at any time before cohort entry.

Statistical analyses

We used descriptive statistics to summarise the characteristics of the cohort. Crude incidence of breast cancer and 95% confidence intervals based on the Poisson distribution were calculated for the entire cohort, and separately for GLP-1 analogues and DPP-4 inhibitors. For the primary analysis, we used a time dependent Cox proportional hazards model to estimate hazard ratios and 95% confidence intervals of breast cancer associated with the use of GLP-1 analogues compared with DPP-4 inhibitor use. All models were adjusted for the potential confounders listed above.

Secondary analyses

We conducted three secondary analyses. The first assessed the risk associated with the most commonly used individual GLP-1 analogues (exenatide and liraglutide). The second assessed whether there was a duration-response association between cumulative duration of use of GLP-1 analogue and breast cancer incidence according to four predefined categories (≤1 year, 1.1-2 years, 2.1-3 years, and >3 years). Thirdly, we assessed the association by time since initiation of GLP-1 analogues according to four predefined categories (1-2 years, 2.1-3 years, 3.1-4 years, and >4 years). In addition, we modelled both duration of use and time since initiation as continuous variables, using a restricted cubic spline model with five knots to produce a smooth curve of the hazard ratio as a function of these time variables.[21 22]

Sensitivity analyses

We conducted eight sensitivity analyses to assess the robustness of our findings:

- Given uncertainties related to the length of the latency time window, we repeated the primary analysis by lengthening the exposure lag period to two years.
- Because GLP-1 analogues are contraindicated among patients with renal failure, we repeated the primary analysis by also excluding patients with a history of renal disorders at any time before cohort entry and censoring on new diagnoses during follow-up.
- Because both GLP-1 analogues and DPP-4 inhibitors are incretin based treatments (and thus share similar mechanisms of action), we repeated the primary analysis using an alternate comparator group consisting of sulfonylureas. A similar analysis was also performed comparing DPP-4 inhibitors with sulfonylureas.
- We repeated the primary analysis using multiple imputation for variables with missing values (supplementary methods 1).[23 24]
- We repeated the primary analysis also adjusting for the use of other glucose lowering drugs (including metformin, glyburide, other sulfonylureas, thiazolidinediones, insulin glargine, other insulins, and other glucose lowering drugs) during follow-up. For this analysis, these glucose lowering drugs were entered as non-mutually exclusive, time varying variables (lagged by one year) in addition to the main exposure variable.
- As another way to control for confounding, we repeated the analysis by stratifying the model in groups based on disease risk score (supplementary methods 2).[25 26]
- To address any time dependent residual confounding during follow-up, we repeated the analysis using a marginal structural Cox proportional hazards model, which adjusts for time dependent confounding associated with time varying exposures (supplementary methods 3).[27 28]
- We conducted an analysis accounting for competing risk due to death using the subdistribution model proposed by Fine and Gray.[29]

Analyses investigating detection bias

Detection bias is a non-random type of information bias in which one exposure group might have a greater or lower opportunity of being screened for the outcome than another exposure group.[30] To investigate the potential effect of detection bias on the findings, we conducted four analyses. Firstly, we repeated the primary analysis by removing the lag period (that is, to capture the early events after treatment initiation). Secondly, we repeated the primary analysis but restricted the outcome definition to malignant cancers and censoring on in situ breast cancers. Thirdly, we used inverse probability of screening weighting[31] to account for the possibility that GLP-1 analogue users might have characteristics that increase or decrease their probability of undergoing mammography screening during follow-up (supplementary methods 4). Finally, we stratified the cohort based on the presence of at least one mammography screening in the three years before cohort entry (as per UK guidelines).[32] For this analysis, we restricted the cohort to patients with at least three years of medical history before cohort entry in the CPRD, and estimated hazard ratios separately for patients with and without a screening history.[33] All analyses described above were conducted with SAS version 9.4 (SAS institute).

Patient involvement

Our study was a secondary data analysis and did not include patients as study participants. No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. The results will be disseminated to the general public through the public relations department of the Lady Davis Institute of the Jewish General Hospital, Montreal, Canada.

Results

The cohort included 44 984 patients (fig 1), followed for a mean of 3.5 years (standard deviation 2.2). Overall, there were 549 incident events of breast cancer during 155 071 person years of follow-up, generating a crude incidence of 3.5 (95% confidence interval 3.3 to 3.8) per 1000 person years. A total of 2473 (5.5%) patients were prescribed GLP-1 analogues during the study period, which included 1071 (43.3%) liraglutide users, 792 (32.0%) exenatide users, 98 (4.0%) lixisenatide users, and 512 (20.7%) who used multiple GLP-1 analogues during the follow-up period.

Table 1 presents baseline characteristics for the cohort, and by use of GLP-1 analogues, DPP-4 inhibitors, and other glucose lowering drugs at cohort entry. Compared with DPP-4 inhibitor users, GLP-1 analogue users were younger, less likely to have had alcohol related disorders, and more likely to be past smokers. GLP-1 analogue users were also more likely to have a higher body mass index, have a higher haemoglobin A1c level, and have used other glucose lowering drugs. Finally, GLP-1 analogue users were more likely to have used hormone replacement therapy and oral contraceptives, but less likely to have certain diabetes related complications and previous cancers.

Table 2 shows the results of primary and secondary analyses. Compared with DPP-4 inhibitor use, use of GLP-1 analogues was not associated with an overall increased risk of breast cancer (4.4 *v* 3.4 per 1000 person years; adjusted hazard ratio 1.40 (95% confidence interval 0.91 to 2.16)). We found similar hazard ratios when analysing liraglutide and exenatide separately (hazard ratio 1.51 (95% confidence interval 0.83 to 2.75) and 1.33 (0.73 to 2.42), respectively). The model did not generate a stable hazard ratio for exposure to lixisenatide and combinations of the above, owing to few exposed events (n=5).

In secondary analyses, 2.1 to 3 years of GLP-1 analogue use was associated with an increased risk of breast cancer (hazard ratio 2.66 (95% confidence interval 1.32 to 5.38)), with the hazard ratio returning to the null after more than three years of use (0.98 (0.24 to 4.03)). We observed a similar pattern with time since initiation, where the hazard ratio was highest at 3.1-4 years after initiation (2.62 (1.37 to 4.99)), and retuned closer to the null after more than four years (1.14 (0.49 to 2.66)). These patterns were also observed in the restricted cubic spline analyses (supplementary figs 1 and 2).

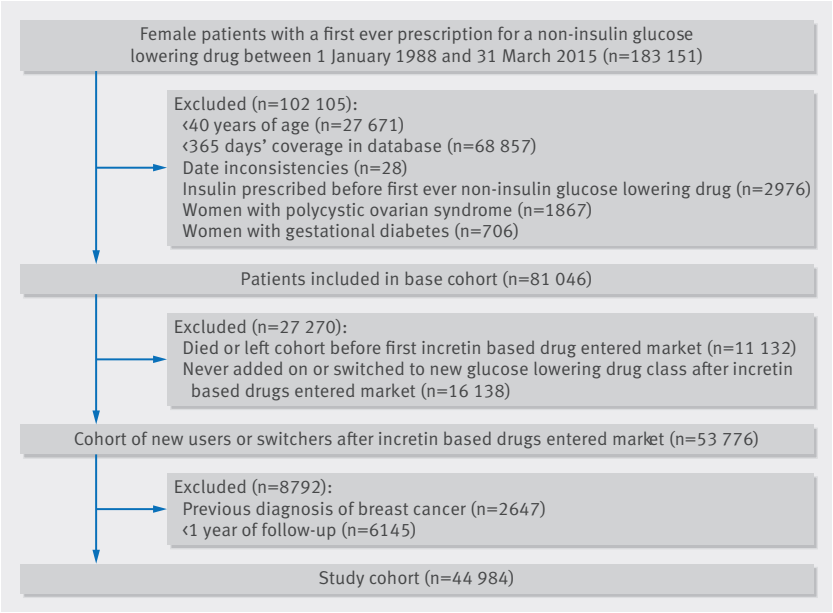

Fig 1 | Study flow diagram describing the construction of the base and study cohorts

Sensitivity analyses

Results of the sensitivity analyses are summarised in figure 2 and presented in supplementary tables 1-9. Overall, nearly all sensitivity analyses generated findings that were consistent with those of the primary analysis. An exception was the two year exposure lag analysis that led to a higher point estimate (hazard ratio 1.63 (95% confidence interval 1.00 to 2.65)).

Analyses investigating detection bias

The analyses investigating possible detection bias are summarised in figure 3 and presented in supplementary tables 10-13. Removing the exposure lag window attenuated the hazard ratio (1.12 (95% confidence interval 0.76 to 1.63)), whereas restricting the event definition to malignant breast cancers did not materially change the hazard ratio (1.47 (0.94 to 2.29)). Overall, the mammography screening rate was higher among GLP-1 analogue users than DPP-4 inhibitor users (18.6 (95% confidence interval 17.7 to 19.5) *v* 13.5 (13.1 to 14.0) per 100 person years, respectively). Adjusting the models for the inverse probability of screening did not materially change the hazard ratio (1.36 (95% confidence interval 0.75 to 2.48)). By contrast, we observed an increased risk of breast cancer among patients with no history of mammography screening (hazard ratio 1.94 (95% confidence interval 1.08 to 3.50)) but no association among those with such a history (0.88 (0.45 to 1.75)).

Discussion

Principal findings

To our knowledge, this is the first observational study to investigate the association between the use of GLP-1 analogues and the risk of breast cancer in women with type 2 diabetes. In this study, the use of GLP-1 analogues was not associated with an overall increased risk of breast cancer. In secondary analyses, associations were observed with two to three years of use and with three to four years since initiation of treatment, but the asso-

doi: 10.1136/bmj.i5340 | *BMJ* 2016;355:i5340 | the bmj

Table 1 | Baseline demographic and clinical characteristics of study cohort and stratified by drug use at cohort entry

Characteristic	Entire cohort	Subgroups		
		Use of GLP-1 analogues	Use DPP-4 inhibitors	Use of other glucose lowering drugs
Total (No)	44 984	498 (1.1)	2422 (5.4)	42 064 (93.5)
Age (years; mean (SD))	64.8 (12.0)	59.8 (8.4)	67.8 (10.4)	64.7 (12.0)
Alcohol related disorders	4817 (10.7)	64 (12.9)	375 (15.5)	4378 (10.4)
Smoking status				
Current	6405 (14.2)	—*	—*	6094 (14.5)
Past	13 125 (29.2)	193 (38.8)	741 (30.6)	12 191 (29.0)
Never	25 331 (56.3)	258 (51.8)	1415 (58.4)	23 658 (56.2)
Unknown	123 (0.3)	—*	—*	121 (0.3)
Body mass index				
<25	4774 (10.6)	—*	254 (10.5)	4516 (10.7)
25-30	11 492 (25.6)	27 (5.4)	583 (24.1)	10 882 (25.9)
≥30.0	27 933 (62.1)	467 (93.8)	1578 (65.2)	25 888 (61.5)
Unknown	785 (1.8)	—*	7 (0.3)	778 (1.9)
Haemoglobin A1c				
≤7.0%	7669 (17.1)	69 (13.9)	304 (12.6)	7296 (17.3)
7.1-8.0%	13 158 (29.3)	103 (20.7)	801 (33.1)	12 254 (29.1)
>8.0%	17 900 (39.8)	321 (64.5)	1291 (53.3)	16 288 (38.7)
Unknown	6257 (13.9)	5 (1.0)	26 (1.1)	6226 (14.8)
Duration of treated diabetes (years; mean (SD))	1.4 (3.0)	7.8 (4.0)	7.6 (3.9)	1.0 (2.4)
Neuropathy	4792 (10.7)	134 (26.9)	625 (25.8)	4033 (9.6)
Renal disease	8848 (19.7)	107 (21.5)	745 (30.8)	7996 (19.0)
Retinopathy	9254 (20.6)	236 (47.4)	1243 (51.3)	7775 (18.5)
Peripheral arteriopathy	1390 (3.1)	14 (2.8)	119 (4.9)	1257 (3.0)
Unique glucose lowering drugs (No; mean (SD))	0.3 (0.7)	2.1 (0.9)	1.6 (0.8)	0.2 (0.6)
Glucose lowering drugs†				
Metformin	42 217 (93.9)	475 (95.4)	2264 (93.5)	39 478 (93.9)
Sulfonylureas	11 451(25.5)	364 (73.1)	1394 (57.6)	9693 (23.0)
Thiazolidinediones	4442 (9.9)	253 (50.8)	912 (37.7)	3277 (7.8)
Insulins	1411 (3.1)	156 (31.3)	108 (4.5)	1147 (2.7)
Other glucose lowering drugs	515 (1.1)	44 (8.8)	113 (4.7)	358 (0.9)
Oophorectomy	1681 (3.7)	19 (3.8)	107 (4.4)	1555 (3.7)
Cancer	4346 (9.7)	38 (7.6)	274 (11.3)	4034 (9.6)
Unique non-diabetic drugs (No; mean (SD))	9.7 (6.5)	13.6 (7.1)	11.8 (6.6)	9.5 (6.4)
Statins	31 884 (70.9)	441 (88.6)	2219 (91.6)	29 224 (69.5)
Hormonal replacement therapy	13 918 (30.9)	207 (41.6)	894 (36.9)	12 817 (30.5)
Oral contraceptives	6118 (13.6)	78 (15.7)	220 (9.1)	5820 (13.8)

Data are number (%) of patients unless stated otherwise. SD=standard deviation; DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1.
*Numbers <5 are not displayed, as per the confidentiality policies of the Clinical Practice Research Datalink.
†Categories are non-mutually exclusive.

Table 2 | Crude and adjusted hazard ratios for the association between use of GLP-1 analogues and risk of breast cancer

Exposure*	No of breast cancer events	No of person years	Incidence (95% CI) per 1000 person years	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)†
DPP-4 inhibitors	68	19 906	3.4 (2.7 to 4.3)	1.00 (reference)	1.00 (reference)
GLP-1 analogues	31	6983	4.4 (3.0 to 6.3)	1.29 (0.85 to 1.98)	1.40 (0.91 to 2.16)
Type of GLP-1 analogue					
Exenatide only	13	3090	4.2 (2.2 to 7.2)	1.23 (0.68 to 2.23)	1.33 (0.73 to 2.42)
Liraglutide only	13	2724	4.8 (2.5 to 8.2)	1.39 (0.77 to 2.52)	1.51 (0.83 to 2.75)
Other	5	1169	4.3 (1.4 to 10.0)	1.24 (0.50 to 3.07)	1.34 (0.54 to 3.34)
Cumulative duration of GLP-1 analogue use (years)					
≤1	11	2921	3.8 (1.9 to 6.7)	1.10 (0.58 to 2.09)	1.21 (0.64 to 2.30)
1.1-2	—§	—§	3.8 (1.7 to 7.2)	1.10 (0.55 to 2.20)	1.18 (0.59 to 2.38)
2.1-3	9	1051	8.6 (3.9 to 16.3)	2.49 (1.24 to 5.01)	2.66 (1.32 to 5.38)
>3	—§	—§	3.2 (0.4 to 11.5)	0.92 (0.22 to 3.75)	0.98 (0.24 to 4.03)
Time since first GLP-1 analogue use (years)					
1-2	5	2237	2.2 (0.7 to 5.2)	0.66 (0.27 to 1.64)	0.72 (0.29 to 1.78)
2.1-3	9	1775	5.1 (2.3 to 9.6)	1.47 (0.73 to 2.94)	1.59 (0.79 to 3.21)
3.1-4	11	1324	8.3 (4.1 to 14.9)	2.42 (1.28 to 4.58)	2.62 (1.37 to 4.99)
>4	6	1647	3.6 (1.3 to 7.9)	1.05 (0.45 to 2.45)	1.14 (0.49 to 2.66)

DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1.
*Use of other diabetes drugs (generating 450 breast events) were considered in the models for proper estimation of effects, but not presented in the table.
†Adjusted for age, year of cohort entry, body mass index, smoking status, alcohol related disorders, haemoglobin A1c, duration of treated diabetes (measured at cohort entry); use of statins, hormonal replacement therapy, and oral contraceptives (measured at any time before cohort entry); presence of microvascular complications of diabetes (neuropathy, renal disease, retinopathy, and peripheral arteriopathy; measured at any time before study cohort entry); the number of unique glucose lowering drugs received in the year before cohort entry; previous cancer diagnosis (excluding non-melanoma skin cancer), previous oophorectomy, and the total number of unique non-diabetic drugs prescribed in the year before cohort entry.
§Cells with less than five observations are not displayed, as per the confidentiality policies of the Clinical Practice Research Datalink.

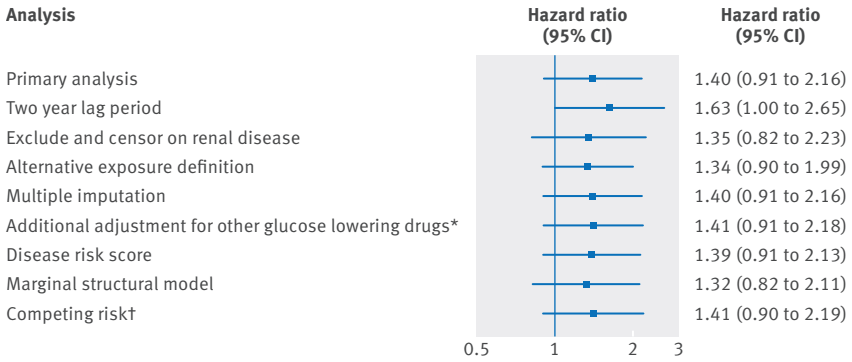

Fig 2 | **Forest plot summarising results of the primary and sensitivity analyses assessing the association between GLP-1 analogue use and breast cancer incidence. *Other glucose lowering drugs entered as non-mutually time varying covariates in addition to the original three level exposure variable. †Estimate is a subdistribution hazard ratio**

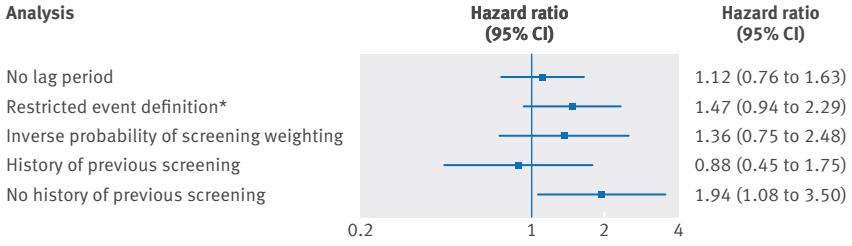

Fig 3 | **Forest plot summarising results of the analyses investigating possible detection bias of breast cancer with GLP-1 analogue use. *Event definition restricted to women with malignant breast cancers**

ciations returned closer to the null with longer durations of use and times since initiation. Although these atypical duration patterns are compatible with a possible tumour promoter effect, they are likely a result of increased detection.

Comparison with previous studies

Supporting the hypothesis of increased detection are the results of the recent LEADER trial in which no imbalance in breast cancer events was observed between patients randomised to liraglutide versus placebo.[7] Although not designed to investigate this safety endpoint, the LEADER trial had a longer follow-up period than previous randomised controlled trials (<1 year), suggesting that initial imbalances in breast cancer might have been the result of a transient detection bias. This result is consistent with those of our study, where associations were observed with two to three year durations of use and three to four years since initiation of GLP-1 analogue use, but the estimates returned closer to the null with longer durations. Furthermore, in analyses investigating the possibility of detection bias, the association was limited to those women with no history of mammography screening—a finding that is compatible with a possible enhanced detection of prevalent disease.

The mechanism for this possible detection bias is not well understood. Although it has been proposed that weight loss induced by GLP-1 analogues could lead to enhanced detection of breast lumps and increased uptake and accuracy of mammography, evidence supporting this hypothesis is lacking,[34 35] and thus additional studies are needed to investigate this hypothesis. Given the observational nature of this study, body weight was not recorded in a systematic fashion, and therefore it was not possible to evaluate the effect of rapid weight loss on the detection of breast cancer. However, it would be of interest to perform such analyses using data from recent large randomised controlled trials of GLP-1 analogues (eg, SCALE[6] and LEADER[7] trials), where body weight was measured in a systematic fashion before randomisation and during follow-up.

Although detection bias is a likely explanation for the observed results, a tumour promoter effect of GLP-1 analogues cannot be ruled out. GLP-1 analogues can promote tumour growth via increased expression of fibroblast growth factor 7 (FGF7).[9] GLP-1 receptors have been located on human breast tissue,[8] and FGF7 is known to be an important paracrine growth factor within the breast.[36] Moreover, its receptor FGFR2 is overexpressed in human breast cancer tissue[10] and is known to be a breast cancer susceptibility gene; its variants associated with breast cancer risk.[37] Thus, the interaction between GLP-1 analogues and the FGF7/FGFR2 axis could stimulate proliferation of a subset of early breast cancers. Additional studies are needed to determine the exact mechanisms through which GLP-1 analogues might increase the risk of breast cancer.

Strengths and limitations

This study has several strengths. Firstly, the use of a new user design minimised biases related to the inclusion of prevalent users.[38] Secondly, we used a time dependent exposure definition, and the exposures were lagged for latency purposes. Additionally, the models were

doi: 10.1136/bmj.i5340 | *BMJ* 2016;355:i5340 | the bmj

adjusted for several potential confounders, and a marginal structural model analysis was conducted to adjust for potential time dependent confounders, yielding similar results. Finally, with the availability of mammography screening information, we were able to conduct various analyses to investigate possible detection bias.

This study also has some limitations. Prescriptions in the CPRD represent those written by general practitioners, and thus misclassification of exposure is possible. However, since all patients entering the cohort were those newly treated with glucose lowering drugs, misclassification is likely minimal and non-differential between exposure groups. Secondly, given the observational nature of the study, residual confounding from unmeasured or unknown variables (such as family history of breast cancer) is possible. Misclassification of the outcome is also possible, although breast cancer has been shown to be well recorded in the CPRD when compared with the UK National Cancer Data Repository.[14] GLP-1 analogues are relatively new drugs, limiting the potential duration of follow-up (maximum of about 9.5 years), which could be considered too short to investigate cancer risk. Indeed, exposure to GLP-1 analogues yielded a relatively small number of breast cancer events (n=31), thus potentially limiting statistical power. However, the rationale for conducting the present study was based on the imbalances observed in randomised controlled trials, which had relatively short durations (20-56 weeks).[5]

Conclusions

In this population based study, the use of GLP-1 analogues was not associated with an overall increased risk of breast cancer risk, providing some reassurance to patients and clinicians. While the observed duration-response associations might be compatible with a tumour promoter effect, they are likely a result of a transient increase in detection of breast cancers in GLP-1 analogue users.

Contributors: All authors conceived and designed the study, analysed and interpreted the data, and critically revised the manuscript for important intellectual content. LA acquired the data. BMH, HY, RWP, and LA did the analyses. BMH wrote the manuscript and all authors participated in the interpretation of the results and critical revision of the manuscript. LA is the guarantor.

Funding: This study was funded by a foundation grant from the Canadian Institutes of Health Research. The sponsor had no influence on design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from the Canadian Institutes of Health Research for the submitted work; RWP holds the Albert Boehringer I chair and is the recipient of a Chercheur-National career award from the Fonds de Recherche du Quebec-Santé (FRQS; Quebec Foundation for Health Research); RWP also reports personal fees from Pfizer, Novartis, Abbvie, and Amgen, outside the submitted work; LA is the recipient of a Chercheur-Boursier career award from the FRQS; all other authors have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study protocol was approved by the independent scientific advisory committee of the Clinical Practice Research Datalink (protocol number 16_096R) and by the research ethics board of Jewish General Hospital, Montreal, Quebec, Canada.

Data sharing: No additional data available.

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supplementary appendix: Additional material