Long-Term Use of Long-Acting Insulin Analogs and Breast Cancer Incidence in Women With Type 2 Diabetes

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ABSTRACT

Purpose
The association between long-acting insulin analogs and increased breast cancer risk is uncertain, particularly with the short follow-up in previous studies. We assessed this risk long term in women with type 2 diabetes.

Methods
A population-based cohort of women 40 years or older, all of whom were treated with long-acting (glargine, detemir) or neutral protamine Hagedorn (NPH) insulin between 2002 and 2012, was formed using the United Kingdom's Clinical Practice Research Datalink. Women were followed until February 2015 or breast cancer diagnosis. Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) and 95% CIs of incident breast cancer, comparing long-acting insulin analogs with NPH overall, as well as by duration and cumulative dose.

Results
The cohort included 22,395 women who received insulin treatment, with 321 incident breast cancer events occurring during up to 12 years of follow-up (incidence rate 3.3 per 1,000 person-years). Compared with NPH insulin, insulin glargine was associated with an increased risk of breast cancer (HR, 1.44; 95% CI, 1.11 to 1.85), mainly increasing 5 years after glargine initiation (HR, 2.23; 95% CI, 1.32 to 3.77) and after $>$ 30 prescriptions (HR, 2.29; 95% CI, 1.26 to 4.16). The risk was particularly elevated among prior insulin users (HR, 1.53; 95% CI, 1.10 to 2.12) but not for new users, which included fewer patients and for which one cannot rule out an HR of 1.81. The risk associated with insulin detemir was not significantly elevated (HR, 1.17; 95% CI, 0.77 to 1.77).

Conclusion
Long-term use of insulin glargine is associated with an increased risk of breast cancer in women with type 2 diabetes. The risk associated with insulin detemir remains uncertain because there are fewer users of this insulin.

INTRODUCTION

Basal insulins, which include neutral protamine Hagedorn (NPH) insulin and the long-acting insulin analogs glargine and detemir, are commonly used to treat patients with type 1 diabetes and advanced type 2 diabetes.[1,2] Although long-acting insulin analogs reduce the occurrence of nocturnal hypoglycemia,[1,2] there are concerns that their use may increase the risk of breast cancer. Indeed, experimental studies have shown that long-acting insulin analogs have stronger binding affinities to the insulin receptor family; this is a proposed mechanism for the increased cellular proliferation and inhibition of apoptosis observed primarily with breast cancer cells.[3-5]

Several observational studies have assessed whether insulin glargine is associated with an increased risk of breast cancer,[6-19] with conflicting results. These studies had a number of methodologic limitations, including prevalent user bias, time-related biases and, most importantly, durations of follow-up that were too short to provide sufficient latency.[20] Furthermore, few studies assessed the association between insulin detemir and breast cancer incidence. Finally, the Outcomes Reduction Insulin Glargine Intervention (ORIGIN) randomized trial, which adjudicated cancer outcomes, had insufficient power for site-specific cancers such as breast and also had too short a follow-up for the necessary latency.[21] Thus, the relationship between long-acting insulin analogs and breast cancer incidence remains uncertain

and, to date, the US Food and Drug Administration finds that the evidence is inconclusive and suggests that more epidemiologic data are needed.[22]

Therefore, now that these insulins have been on the market for a longer period of time, we assessed whether the long-term use of long-acting insulin analogs, compared with the use of NPH insulin, is associated with an increased risk of breast cancer in women with type 2 diabetes receiving insulin therapy.

METHODS

Data Source

The study was conducted using the United Kingdom (UK) Clinical Practice Research Datalink (CPRD).[23] The CPRD includes approximately 700 practices with > 14 million patients and has been shown to be representative of the UK general population.[23] This study was approved by the Independent Scientific Advisory Committee of CPRD (protocol number 15_005R), Institutional Review Board of McGill University (A11-M114-14B), and Research Ethics Board of Jewish General Hospital in Montreal, Quebec, Canada.

Study Sample

We first identified a base population of all women 40 years of age or older who received at least one prescription for any type of insulin (rapid-acting insulin analogs, short-acting insulins, intermediate-acting insulins, long-acting insulin analogs, premixed insulin, and animal insulin) between January 1, 1988, and December 31, 2012. Because women with type 1 diabetes have a different pathophysiology than women with type 2 diabetes,[24] we restricted the cohort to women 40 years or older at the time of base cohort entry; type 2 diabetes is more likely to be diagnosed in the elderly population.[25,26] We excluded women with < 1 year of medical history in the CPRD, as well as those with a previous diagnosis of gestational diabetes, before base cohort entry. We then included only women with at least one prescription for basal insulin (glargine, detemir, or NPH) between September 1, 2002 (the year the first long-acting insulin analog, glargine, entered the UK market), and December 31, 2012.

The study cohort was formed using a hierarchical approach to define patients in the glargine, detemir, and NPH study cohorts. We first identified women with at least one long-acting insulin analog prescription, either glargine or detemir, after September 1, 2002. Study cohort entry for these users of long-acting insulin analogs was taken as the date of the first long-acting insulin analog prescription. To ensure that the comparator NPH insulin users (selected after September 1, 2002) had a starting time point comparable to that of the long-acting insulin analog users, we distinguished between the women who were receiving their first long-acting insulin analog prescription without having previously received NPH or other insulins (new insulin users) and the ones who switched from NPH or other insulins to a long-acting insulin analog (prior insulin users).[27] For the comparator for the new users of long-acting insulin analogs, we identified women whose NPH prescription was after September 1, 2002, and who had no previous use of any insulin (ie, first ever), with the date of this first-ever NPH insulin prescription defining the study cohort entry date. For women whose NPH insulin prescription was after September 1, 2002, and was not the first ever, we randomly selected for each subject one NPH insulin prescription between September 1, 2002, and December 31, 2012. The date of the randomly selected NPH insulin prescription was the study cohort entry for this prevalent NPH user. After the study cohort entry date was identified for each woman, we excluded all women with a history of cancer any time before study cohort entry. All subjects were followed from study cohort entry until February 28, 2015.

Exposure Definition

The primary exposure definition was based on the first insulin defining the study cohort, either a long-acting insulin analog or NPH insulin (referent), which is analogous to an intent-to-treat approach. For our secondary exposure, we also evaluated the duration of use (from the long-acting insulin analog or NPH insulin prescription defining the study cohort entry date) and the cumulative dose (defined as the cumulative number of insulin glargine and NPH prescriptions) as time-dependent measures. More specifically, we cumulated time and prescriptions for which the patient was defined at cohort entry. On the basis of this time-dependent exposure, it was possible that patients could contribute person-time to each duration or dose category.

Outcome Definition and Follow-Up

Women were followed from study cohort entry to an incident diagnosis of primary invasive breast cancer, end of CPRD registration, death, or study end date (February 28, 2015), whichever came first.

Covariates

Confounders known to be risk factors for cancer were identified before study cohort entry. We included age, calendar year of study cohort entry, excessive alcohol use (alcohol-related diseases or alcoholism screening), smoking status, body mass index (BMI; kg/m^2), glycated hemoglobin (HbA1c), diabetes duration at study cohort entry (time between the first of the dates of first antidiabetic medication, diagnosis of type 2 diabetes, or HbA1c value ≥ 6.5% and study cohort entry date), prior use of insulin and duration of prior insulin use, noninsulin antidiabetic medications use, Deyo's Charlson comorbidity score (excludes previous cancers),[28] and other medication use (including hormone replacement therapy, statins, aspirin, and nonsteroidal anti-inflammatory medications). Noninsulin antidiabetic medications included metformin, sulfonylureas, thiazolidinediones, meglitinides, dipeptidyl-peptidase-4 inhibitors, glucagon-like-peptide-1 analogs, alpha-glucosidase inhibitors, guar gum, and sodium/glucose cotransporter-2 inhibitors. In 2004, the Quality and Outcomes Framework was created to incentivize physicians to record information on common chronic diseases, public health concerns, and preventative measures.[23] Hence, smoking status and BMI measures are > 90% complete in our study.

Statistical Analysis

The crude incidence rates of breast cancer diagnosed during follow-up and 95% CIs were estimated by cumulating the person-time over the follow-up using the Poisson distribution. We used the Kaplan-Meier approach to compute the cumulative incidence of breast cancer over time for each exposure group. We also computed the mean number of insulin prescriptions for each insulin type.

For the primary analysis, we used the Cox proportional hazards model, with duration of follow-up as the timescale, to estimate the crude and adjusted hazard ratios (HRs) and 95% CIs of incident breast cancer comparing users of long-acting insulin analogs with users of NPH insulin. Adjustment was on the basis of all covariates identified before study cohort entry. We included an indicator for missing data in the smoking, BMI, and HbA1c categorical variables because the extent of missing data was minimal (approximately 5%). For the duration and dose-response analyses, we used a time-dependent Cox model to estimate the crude and adjusted HRs and 95% CIs. These analyses were first performed on the basis of predefined categories of duration of use (< 3, 3 to 5, and > 5 years) and the number of prescriptions for the insulins under study (< 10, 10 to 30, > 30 prescriptions). Moreover, we compared the same levels of duration and dose of long-acting insulin analogs with NPH insulin (eg, < 3 years of insulin glargine use with < 3 years of NPH insulin use) by contrasting the regression coefficients in the time-dependent Cox models. Restricted cubic splines were also used to estimate the HR as a continuous function of duration since first long-acting insulin analogs.

Sensitivity analyses were conducted to assess the robustness of the estimates. First, we stratified the analyses according to prior insulin use. Second, to refute misclassification bias, we included a 1 to 3–year lag period to account for cancer latency. Third, to assess detection bias, we performed stratified analyses according to age (< 50, 50 to 70, and > 70 years) and prior mammography screening. Finally, because patients with type 2 diabetes have increased mortality, we performed a competing risk analysis from all-cause death using the subdistribution hazards models developed by Fine and Gray.[29]

All data analyses were performed using SAS version 9.4 statistical software (SAS Institute, Cary, NC), including the restricted cubic splines fit using the SAS macro developed by Heinzl and Kaider.[30] Forest plots were constructed with the meta package from R version 3.3.1 (R Development Core Team, Vienna, Austria).

RESULTS

A total of 22,395 women formed the cohort, which included 9,575, 3,271, and 9,549 users of insulin glargine, detemir, and NPH, respectively (Fig 1). During the up to 12 years of follow-up (mean, 4.4 years), 321 incident breast cancers were diagnosed, corresponding to a crude incidence rate of 3.3 per 1,000 person-years. On average, women in the insulin glargine, detemir, and NPH exposure groups received 5.4, 5.4, and 5.8 prescriptions for these insulins per year, respectively, over the entire follow-up. The baseline characteristics of long-acting insulin analog users, compared with NPH insulin, were younger, shorter diabetes duration, used more first- and second-line antidiabetic medications, had lower prior duration of insulin use, lower BMI, and fewer comorbidities, but had higher HbA1c and more alcohol-related diseases (Table 1).

Women who received insulin glargine, compared with NPH insulin, had a higher incidence of breast cancer (adjusted HR, 1.44; 95% CI, 1.11 to 1.85; Table 2). The risk of breast cancer started to increase 5 years after insulin glargine initiation (HR, 2.23; 95% CI, 1.32 to 3.77; Appendix Table A1, online only). The crude cumulative

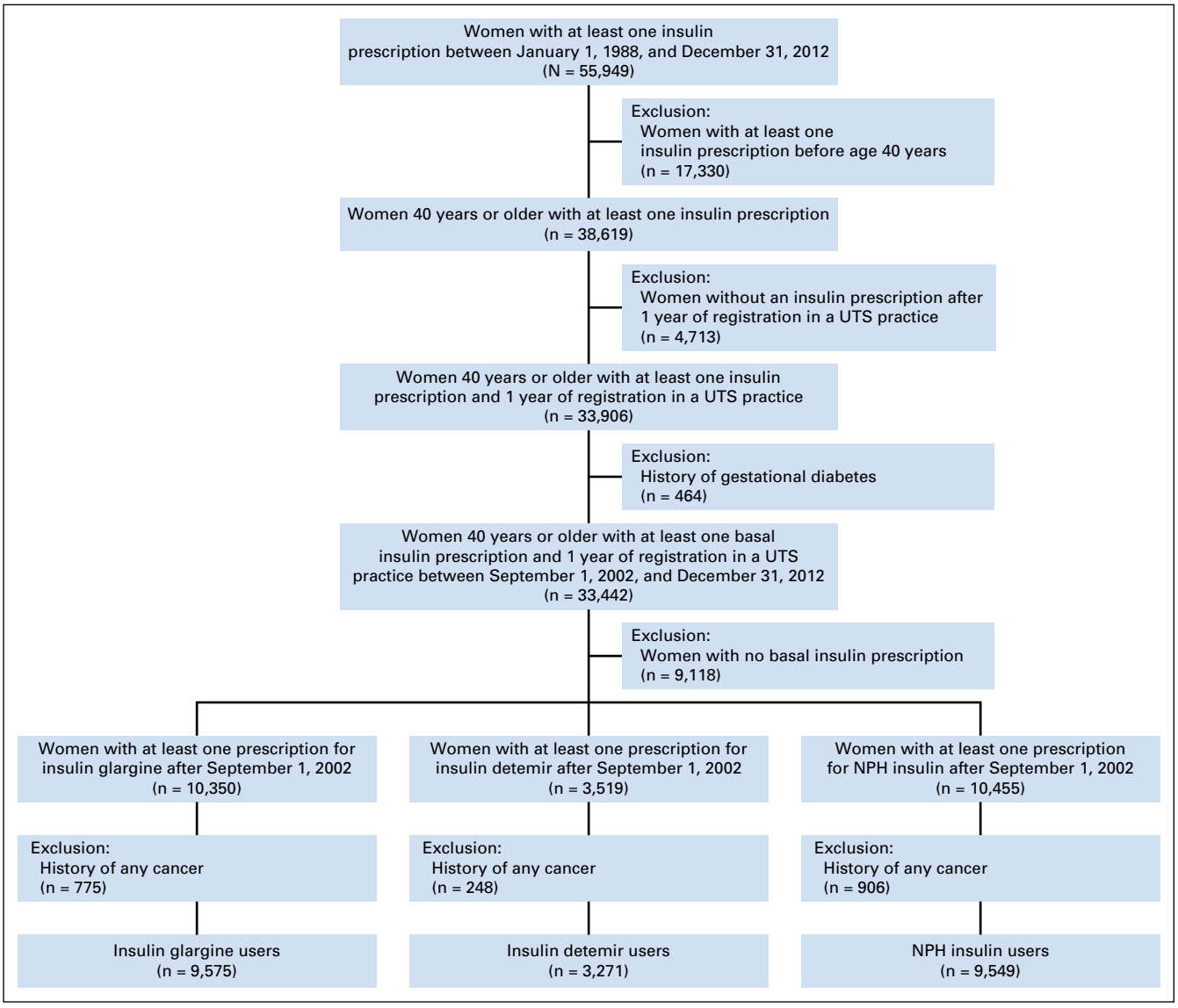

Fig 1. Flow chart describing the selection of 22,395 women 40 years or older with at least one prescription for any basal insulin between September 1, 2002, and December 31, 2012. NPH, neutral protamine Hagedorn; UTS, up to standard.

Table 1. Baseline Characteristics of Study Cohort of Women With at Least One Prescription for Insulin Glargine, Detemir, or Neutral Protamine Hagedorn, According to Insulin Exposure at Study Cohort Entry

Covariate	Glargine	Detemir	NPH
No. of women	9,575	3,271	9,549
Age, years*	64.9 (12.9)	63.5 (12.2)	70.3 (11.6)
Calendar year*			
2002-2005	2,901 (30.3)	149 (4.6)	4,123 (43.2)
2006-2008	3,778 (39.5)	1,646 (50.3)	3,066 (32.1)
2009-2012	2,896 (30.3)	1,476 (45.1)	2,360 (24.7)
Excessive alcohol use†	421 (4.4)	175 (5.4)	330 (3.5)
Smoking status†			
Ever	3,205 (33.5)	1,106 (33.8)	3,096 (32.4)
Never	6,245 (65.2)	2,157 (65.9)	6,124 (63.1)
Unknown	125 (1.3)	8 (0.2)	329 (3.5)
BMI, kg/m^2‡			
25	2,066 (21.6)	621 (19.0)	1,493 (15.6)
25-30	2,699 (28.2)	850 (26.0)	2,440 (25.6)
30	4,296 (44.9)	1,711 (52.3)	4,575 (47.9)
Unknown	514 (5.4)	89 (2.7)	1,041 (10.9)
Hemoglobin A1c, %§			
6.5	332 (3.5)	94 (2.9)	695 (7.3)
6.5-8.0	1,964 (20.5)	662 (20.2)	2,766 (29.0)
8.0	6,750 (70.5)	2,414 (73.8)	5,057 (53.0)
Unknown	529 (5.5)	101 (3.1)	1,031 (10.8)
Diabetes duration, years*	8.2 (5.4)	8.5 (5.6)	9.3 (5.6)
Prior insulin use	5,427 (56.7)	2,009 (61.4)	6,897 (72.2)
Prior duration of insulin use, years*	2.8 (4.3)	3.1 (4.5)	4.3 (4.7)
Noninsulin diabetes medication use§‖			
Metformin	5,830 (60.9)	2,046 (62.6)	4,837 (50.7)
Sulfonylurea	4,661 (48.7)	1,495 (45.7)	2,930 (30.7)
Thiazolidinedione	2,048 (21.4)	728 (22.3)	977 (10.2)
Other¶	1,177 (12.3)	474 (14.5)	743 (7.8)
Charlson comorbidity score#			
≤ 1	5,052 (52.8)	1,612 (49.3)	4,907 (51.4)
2-3	3,376 (35.3)	1,246 (38.1)	3,410 (35.7)
3	1,147 (12.0)	413 (12.6)	1,232 (12.9)
Hormone replacement therapy§	2,876 (30.0)	1,040 (31.8)	2,136 (22.4)
Statins§	6,795 (71.0)	2,547 (77.9)	6,392 (66.9)
Aspirin§	4,722 (49.3)	1,638 (50.1)	5,269 (55.2)
Nonsteroidal anti-inflammatory drugs§	3,631 (37.9)	1,286 (39.3)	3,519 (36.9)

Abbreviations: BMI, body mass index; NPH, neutral protamine Hagedorn.
NOTE. Data are presented as the mean (standard deviation) or no. (%) unless otherwise specified.
*Measured at study cohort entry.
†Measured at any time before study cohort entry.
‡Measured 5 years prior.
§Measured 2 years prior.
‖Not mutually exclusive.
¶Other noninsulin diabetes medications included meglitinides, dipeptidyl-peptidase-4 inhibitors, glucagon-like-peptide-1 analogs, alpha-glucosidase inhibitors, guar gum, and sodium/glucose cotransporter-2 inhibitors.
#Measured 1 year prior.

incidence curves of breast cancer over time are shown for insulin glargine, insulin detemir, and NPH insulin (Appendix Fig A1, online only). The adjusted restricted cubic splines of the HR and 95% CIs as a function of time since initiation of insulin glargine, relative to NPH insulin, are depicted in Fig 2, showing the increase in risk 5 years after initiation.

Table 2 also shows that a cumulative number of insulin glargine prescriptions of at least 30 prescriptions was associated with an increase in the risk of breast cancer (HR, 2.29; 95% CI, 1.26 to 4.16). In contrast, there was no increased risk of breast cancer associated with use of insulin detemir compared with NPH insulin (HR, 1.17; 95% CI, 0.77 to 1.77), nor was an association with duration or dose response observed (Appendix Tables A2 and A3, online only).

In the first sensitivity analysis, the association between insulin glargine and breast cancer was particularly concentrated among prior insulin users (HR, 1.53; 95% CI, 1.10 to 2.12), but not new insulin users (HR, 1.18; 95% CI, 0.77 to 1.81; Appendix Table A4, online only). Similarly, a duration and dose-response association was observed among prior insulin users only (Appendix Tables A1 and A5, online only; Appendix Fig A2, online only). The various sensitivity analyses of the robustness of our estimates are summarized in Fig 3, which shows that the estimates are generally robust. In all of the sensitivity analyses, insulin glargine was associated with an increased risk of breast cancer, with adjusted HRs ranging from 1.44 to 1.93, whereas for insulin detemir the adjusted HRs ranged from 0.79 to 1.44 with wide CIs (Appendix Fig A3, online only).

Table 2. Crude and Adjusted Hazard Ratios of Breast Cancer Associated With Use of Long-Acting Insulin Analogs Compared With Neutral Protamine Hagedorn Insulin Use, In the Entire Insulin Cohort

Exposure	No. of Patients	No. of Events	Person-Years	Incidence Rate (95% CI)*	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)†
Overall use						
NPH	9,549	108	35,077	3.1 (2.5 to 3.7)	1.00 (reference)	1.00 (reference)
Glargine	9,575	176	48,685	3.6 (3.1 to 4.2)	1.19 (0.94 to 1.52)	1.44 (1.11 to 1.85)
Detemir	3,271	37	14,834	2.5 (1.8 to 3.4)	0.81 (0.56 to 1.18)	1.17 (0.77 to 1.77)
No. of prescriptions						
NPH						
< 10	9,549	60	16,136	3.7 (2.9 to 4.8)	1.00 (reference)	1.00 (reference)
10-30	5,133	33	11,306	2.9 (2.1 to 4.1)	1.00 (reference)	1.00 (reference)
> 30	2,293	15	7,635	2.0 (1.2 to 3.3)	1.00 (reference)	1.00 (reference)
Glargine						
< 10	9,575	73	19,871	3.7 (2.9 to 4.6)	0.99 (0.70 to 1.40)	1.15 (0.80 to 1.64)
10-30	6,382	61	17,124	3.6 (2.8 to 4.6)	1.26 (0.82 to 1.92)	1.52 (0.99 to 2.35)
> 30	3,256	42	11,689	3.6 (2.7 to 4.9)	1.85 (1.03 to 3.37)	2.29 (1.26 to 4.16)

Abbreviation: NPH, neutral protamine Hagedorn.
*Per 1,000 person-years.
†The multivariable Cox proportional hazards model was adjusted for the following covariates before study cohort entry: age (years), calendar year, diabetes duration (years), prior duration of insulin use (years), hemoglobin A1c (< 6.5% [reference], 6.5% to 8.0%, > 8.0%, unknown), use of antidiabetic medications versus no use (metformin, sulfonylureas, thiazolidinedione, and others), other medication use versus no use (hormone replacement therapy, statins, aspirin, and nonsteroidal anti-inflammatory medications), body mass index (< 25 [reference], 25 to 30, > 30 kg/m^2, unknown), Charlson comorbidity score (≤ 1 [reference], 2 to 3, > 3), excessive alcohol use versus no use, smoking status (never [reference], ever, unknown).

DISCUSSION

In a large cohort of > 22,000 women with type 2 diabetes treated with insulin, we found that the use of insulin glargine was associated with an increased risk of breast cancer. In the duration and dose-response analyses, we found that the risk of breast cancer increased after ≥ 5 years of insulin glargine use and > 30 insulin glargine prescriptions, respectively. The insulin glargine users were associated with an increased risk of breast cancer among prior insulin users only. Our findings for insulin glargine and breast cancer incidence remained consistent in several sensitivity analyses.

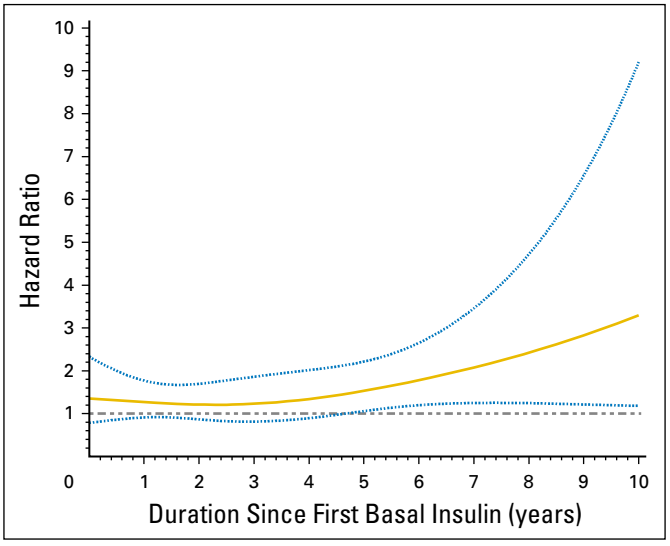

Fig 2. Restricted cubic splines of the adjusted hazard ratio (solid line) and 95% CIs (dotted lines) for breast cancer incidence as a function of duration since first insulin glargine prescription compared with neutral protamine Hagedorn in the entire cohort (gray dashed line represents the reference hazard ratio = value 1).

In contrast, the results between insulin detemir and breast cancer were inconclusive given the smaller sample size and short duration of use as the result of its recent introduction to the UK market.

To date, 14 observational studies have been conducted to evaluate the association between insulin glargine and breast cancer incidence.[6-19] Of these, seven observed an increased risk of breast cancer, with HRs ranging from 1.30 to 3.65.[6,8,12,13,15,17,19] Of these seven studies, three observed an association among new insulin users only.[6,12,17] The variations in the results of these previous studies were attributed to insufficient duration of follow up (< 5 years), prevalent user bias, the use of inappropriate comparators (other insulins), and the lack of lag periods to account for cancer latency.[20] Importantly, one previous study using the same data source and a similar study design observed that women who used insulin glargine ≥ 5 years compared with other insulins were at an increased risk of breast cancer among prior insulin users only (HR, 2.70; 95% CI, 1.10 to 6.50).[19] Although there is some overlap of data with this previous study, our study had a larger number of events among women using insulin glargine (176 *v* 66) and up to 12 years of follow up (mean, 4.4 years). Currently, only three studies have evaluated the relationship between insulin detemir and breast cancer, but these studies had small numbers of breast cancer events and short follow-up.[10,31,32] The ORIGIN trial had important strengths (including adjudication of cancer outcomes), but similar to the other post hoc analyses of randomized controlled trials, it had insufficient power to detect an effect with site-specific cancers such as breast, and it had a relatively short follow-up to assess cancer incidence (< 7 years).[21]

Previous studies have suggested that breast epithelial cells exposed to insulin are at risk for transformation in a stepwise carcinogenesis process.[33,34] More specifically, insulin has been shown to activate members of the insulin-like growth factor (IGF) receptor family to inhibit apoptosis and subsequently prolong the survival of these transformed breast tissue cells.[34] Long-acting insulin analogs are efficacious at controlling HbA1c levels, but

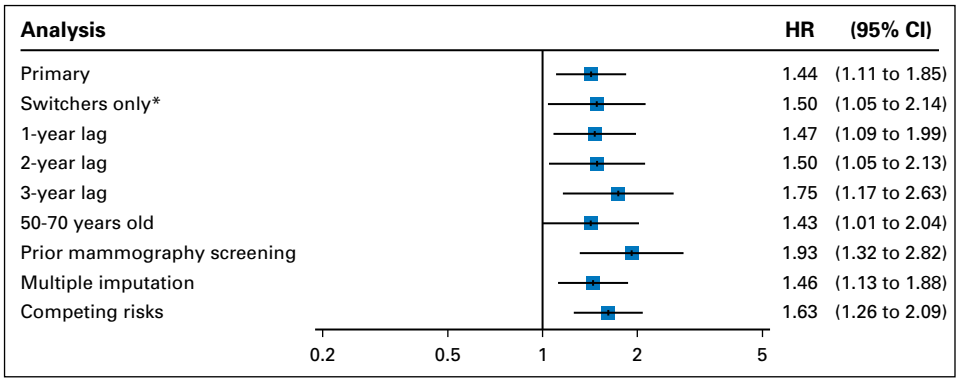

Fig 3. Forest plots of sensitivity analyses for insulin glargine and breast cancer. HR, hazard ratio. (*) Patients who switched from neutral protamine Hagedorn and/or other insulins to insulin glargine before or after 2002.

they have also been shown to have mitogenic effects through the insulin- or IGF receptor–mediated cellular pathways. Although the evidence has not been consistent in the experimental studies, these synthetic insulins have been reported to have altered receptor-binding characteristics, resulting in stronger binding affinity.[35] Furthermore, a majority of experimental studies have been conducted in breast cancer cell lines and have suggested that insulin glargine binds with greater affinity to IGF receptors to activate mitogen-activated protein kinase pathways, which then upregulate cellular proliferation and antiapoptotic effects.[3,4] In contrast, insulin detemir and breast cancer cells have been shown to have less binding affinity.[3,4,35] Albeit, some studies have shown that insulin detemir can still initiate the same mitogenic cellular pathways through the insulin receptor family.[36] Consequently, it is plausible that use of long-acting insulin analogs could increase the risk of breast cancer and have these long-term effects through these altered pharmacokinetics.

Our study has several important strengths. First, unlike previous studies, we had up to 12 years of follow-up. Importantly, we were able to minimize prevalent user bias and account for cancer latency. In addition, given the use of CPRD, we were able to adjust for confounders that are not typically available in health administrative databases, such as BMI and smoking status.

Despite the strengths of our study, it has several limitations. First, like many other observational studies, there is still potential for unmeasured confounding. However, this is unlikely because only a strong unmeasured confounder, with major imbalance between insulin glargine and NPH, would be needed to bias the HR. Second, in our duration and dose-response analyses, the cumulative incidence for long-acting insulin analog users compared with NPH insulin users diverged over time. This decrease could be explained by the changing characteristics of NPH insulin users over time; thus confounding was apparent in the decreased incidence. In addition, long-acting insulin analog users compared with NPH insulin users were younger (64 to 65 *v* 70 years) and within the mammography screening age in the United Kingdom. Consequently, NPH insulin users may be screened less over time, yielding lower incidence. Third, there is potential for outcome misclassification; however, a previous study compared CPRD cancer diagnostic codes with the United Kingdom's cancer registry and observed high concordance ($\geq$ 90%).[37] Moreover, this outcome misclassification would probably be nondifferential with respect to exposure status and potentially bias the results toward the null in the primary analysis. Fourth, our analysis of prior insulin use suggested that the increase in risk with glargine was mainly among patients who had prior insulin use, but not among the initiators; albeit the latter had a wide CI that did not exclude an HR $\leq$ 1.81. This analysis was limited in power, namely because only $<$ 30% of the reference NPH insulin users were insulin initiators. Similarly, the number of users of detemir and the duration of use were also limited by the later entry of this insulin in the market, thus also reducing the power of this analysis. Last, detection bias could have been present in our study. However, our lagged, age-stratified, and prior mammography screening–stratified analyses yielded similar results, which suggests that detection bias alone cannot explain the increased risk of breast cancer among insulin glargine users compared with NPH insulin users.

In conclusion, insulin glargine use was associated with an increased risk of breast cancer in a cohort of women with type 2 diabetes, particularly with long-term use. Despite these findings, the benefits and risks of insulin glargine must be considered by drug regulatory agencies before any changes to clinical practice can be made. Given the fewer number of women and shorter duration of use as the result of its more recent introduction to the UK market, future studies are needed to further evaluate the relationship between long-term use of insulin detemir and breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
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Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Support

Funded in part by infrastructure grants from the Canadian Institutes of Health Research and the Canadian Foundation for Innovation. J.W.W. was a recipient of a Canadian Institutes of Health Research Doctoral Research award at the time the study was being conducted. L.A. is the recipient of a Chercheur-Boursier award from the Fonds de la Recherche du Québec-Santé (FRQS) and a William Dawson Scholar award from McGill University. S.S. is the recipient of the James McGill Professorship award. The sponsors 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.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Long-Term Use of Long-Acting Insulin Analogs and Breast Cancer Incidence in Women With Type 2 Diabetes

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to v

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Employment: Analysis Group
Research Funding: Canadian Institutes of Health Research

Laurent Azoulay
No relationship to disclose

Agnieszka Majdan
Honoraria: Novo Nordisk
Consulting or Advisory Role: Merck
Speakers' Bureau: Janssen Pharmaceuticals

Jean-François Boivin
Consulting or Advisory Role: Bracco Diagnostics
Travel, Accommodations, Expenses: Bracco Diagnostics

Michael Pollak
No relationship to disclose

Samy Suissa
No relationship to disclose

Acknowledgment

We thank Sophie Dell'Aniello, Hui Yin, and Janie Coulombe, who are analysts at the Lady Davis Institute-Jewish General Hospital, for their expertise and time spent consulting on the data management and analysis.

Appendix

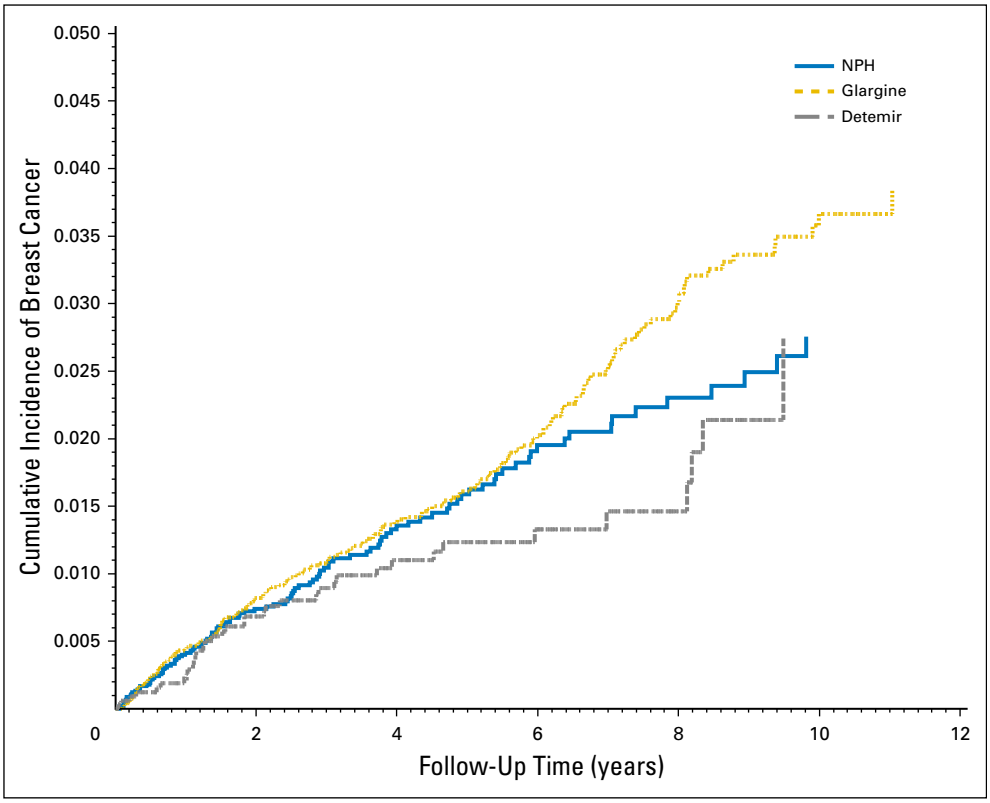

Fig A1. Cumulative incidence of breast cancer curves by insulin. NPH, neutral protamine Hagedorn.

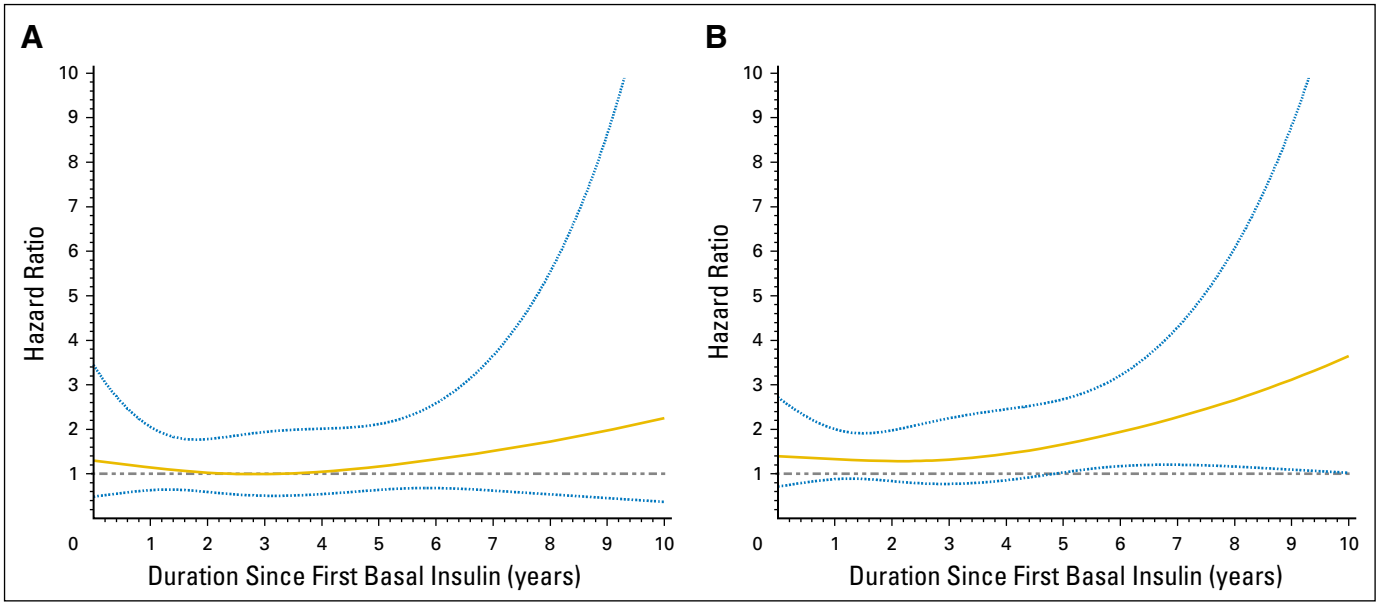

Fig A2. Restricted cubic splines of the adjusted hazard ratio and 95% CIs for breast cancer incidence as a function of duration since first insulin glargine prescription compared with neutral protamine Hagedorn among new (A) and prior insulin users (B), with three knots placed at the 20th (0.9 years), 50th (2.4 years), and 80th (5.8 years) percentile.

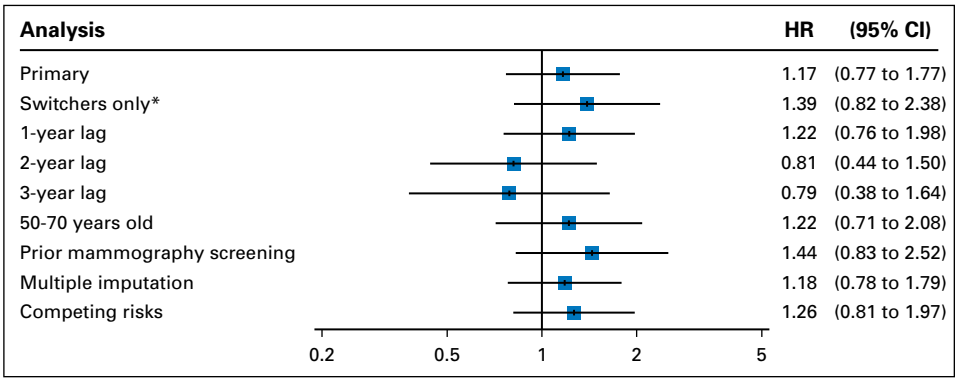

Fig A3. Forest plots of primary and sensitivity analyses for insulin detemir. HR, hazard ratio. (*) Patients who switched from neutral protamine Hagedorn and/or other insulins to insulin detemir before or after 2002.

Table A1. Crude and Adjusted Hazard Ratios of Breast Cancer by Duration Since First Insulin Glargine or Neutral Protamine Hagedorn Prescription at Study Cohort Entry in the Entire Cohort and Among New and Prior Insulin Users

Exposure, No. of Years	No. of Patients	No. of Breast Cancer Cases	Person-Years	Incidence Rate (95% CI)*	Hazard Ratios (95% CI)	
					Crude	Adjusted†
All women						
NPH						
< 3	9,549	70	19,597	4.6 (2.8 to 4.5)	1.00	1.00
3-5	4,386	19	6,944	2.7 (1.7 to 4.3)	1.00	1.00
≥ 5	2,754	19	8,536	2.2 (1.4 to 3.5)	1.00	1.00
Glargine						
< 3	9,575	88	23,842	3.7 (3.0 to 4.5)	1.05 (0.77 to 1.44)	1.25 (0.90 to 1.74)
3-5	6,332	29	10,612	2.7 (1.9 to 3.9)	1.00 (0.56 to 1.79)	1.21 (0.68 to 2.18)
≥ 5	4,391	59	14,231	4.1 (3.2 to 5.4)	1.85 (1.10 to 3.11)	2.23 (1.32 to 3.77)
New insulin users						
NPH						
< 3	2,652	20	6,257	3.2 (2.1 to 5.0)	1.00	1.00
3-5	1,477	7	2,339	3.0 (1.4 to 6.3)	1.00	1.00
≥ 5	941	7	3,148	2.2 (1.1 to 4.7)	1.00	1.00
Glargine						
< 3	4,148	35	10,409	3.4 (2.4 to 4.7)	1.05 (0.61 to 1.83)	1.08 (0.62 to 1.90)
3-5	2,741	13	4,505	2.9 (1.7 to 5.0)	0.97 (0.39 to 2.42)	1.02 (0.40 to 2.59)
≥ 5	1,809	19	5,257	3.6 (2.3 to 5.7)	1.52 (0.64 to 3.61)	1.60 (0.66 to 3.84)
Prior insulin users‡						
NPH						
< 3	6,897	50	13,340	3.7 (2.8 to 4.9)	1.00	1.00
3-5	2,909	12	4,605	2.6 (1.5 to 4.6)	1.00	1.00
≥ 5	1,813	12	5,389	2.2 (1.3 to 3.9)	1.00	1.00
Glargine						
< 3	5,427	53	13,434	3.9 (3.0 to 5.2)	1.08 (0.73 to 1.58)	1.33 (0.88 to 2.00)
3-5	3,591	16	6,107	2.6 (1.6 to 4.3)	1.01 (0.48 to 2.14)	1.24 (0.58 to 2.65)
≥ 5	2,582	40	8,974	4.5 (3.3 to 6.1)	2.03 (1.07 to 3.88)	2.49 (1.28 to 4.81)

Abbreviation: NPH, neutral protamine Hagedorn.
*Per 1,000 person-years.
†The multivariable Cox proportional hazards model was adjusted for the following covariates before study cohort entry: age (years), calendar year, diabetes duration (years), prior duration of insulin use (years), hemoglobin A1c (< 6.5% [reference], 6.5% to 8.0%, > 8.0%, missing), use of antidiabetic medications versus no use (metformin, sulfonylureas, thiazolidinedione, and others), other medication use versus no use (hormone replacement therapy, statins, aspirin, and nonsteroidal anti-inflammatory medications), body mass index (< 25 [reference], 25 to 30, > 30 kg/m^2, missing), Charlson comorbidity score (≤ 1 [reference], 2 to 3, > 3), excessive alcohol use versus no use, smoking status (never [reference], ever, missing).
‡Prior insulin users were defined as women with at least any type of insulin before study cohort entry.

Table A2. Crude and Adjusted Hazard Ratios of Breast Cancer by Duration Since First Insulin Detemir or Neutral Protamine Hagedorn Prescription at Study Cohort Entry

Exposure, No. of Years	No. of Patients	No. of Breast Cancer Cases	Person-Years	Incidence Rate (95% CI)*	Hazard Ratios (95% CI)	
					Crude	Adjusted†
NPH						
3	9,549	70	19,597	4.6 (2.8 to 4.5)	1.00	1.00
3-5	4,386	19	6,944	2.7 (1.7 to 4.3)	1.00	1.00
≥ 5	2,754	19	8,536	2.2 (1.4 to 3.5)	1.00	1.00
Detemir						
3	3,271	25	8,202	3.0 (2.8 to 4.5)	0.86 (0.55 to 1.36)	1.28 (0.78 to 2.10)
3-5	2,139	6	3,442	1.7 (0.8 to 3.9)	0.64 (0.26 to 1.60)	0.91 (0.36 to 2.32)
≥ 5	1,330	6	3,190	1.9 (0.8 to 4.2)	0.80 (0.32 to 2.02)	1.07 (0.42 to 2.74)

Abbreviation: NPH, neutral protamine Hagedorn.
*Per 1,000 person-years.
†The multivariable Cox proportional hazards model was adjusted for the following covariates before study cohort entry: age (years), calendar year, diabetes duration (years), prior duration of insulin use (years), hemoglobin A1c (< 6.5% [reference], 6.5% to 8.0%, > 8.0%, missing), use of antidiabetic medications versus no use (metformin, sulfonylureas, thiazolidinedione, and others), other medication use versus no use (hormone replacement therapy, statins, aspirin, and nonsteroidal anti-inflammatory medications), body mass index (< 25 [reference], 25 to 30, > 30 kg/m^2, missing), Charlson comorbidity score (≤ 1 [reference], 2 to 3, > 3), excessive alcohol use versus no use, smoking status (never [reference], ever, missing).

Table A3. Crude and Adjusted Hazard Ratios of Breast Cancer Associated With Cumulative Dose of Insulin Detemir Compared With Neutral Protamine Hagedorn Insulin in the Entire Insulin Cohort

Exposure, No. of Prescriptions	No. of Patients	No. of Breast Cancer Cases*	Person-Years	Incidence Rate (95% CI)†	Hazard Ratios (95% CI)	
					Crude	Adjusted‡
NPH (reference)						
10	9,549	60	16,136	3.7 (2.9 to 4.8)	1.00	1.00
10-30	5,133	33	11,306	2.9 (2.1 to 4.1)	1.00	1.00
30	2,293	15	7,635	2.0 (1.2 to 3.3)	1.00	1.00
Detemir						
10	3,271	18	6,872	2.6 (1.7 to 4.2)	0.81 (0.47 to 1.39)	1.01 (0.57 to 1.78)
10-30	2,082	14	5,158	2.7 (1.6 to 4.6)	1.17 (0.62 to 2.22)	1.49 (0.77 to 2.87)
30	964	S	2,805	1.8 (0.7 to 4.3)	0.99 (0.36 to 2.76)	1.23 (0.44 to 3.45)

Abbreviation: NPH, neutral protamine Hagedorn.
*Cell numbers of less than five are suppressed (S) in accordance with the confidentiality agreements of Clinical Practice Research Datalink.
†Per 1,000 person-years.
‡The multivariable Cox proportional hazards model was adjusted for the following covariates before study cohort entry: age (years), calendar year, diabetes duration (years), prior duration of insulin use (years), hemoglobin A1c (< 6.5% [reference], 6.5% to 8.0%, > 8.0%, missing), use of antidiabetic medications versus no use (metformin, sulfonylureas, thiazolidinedione, and others), other medication use versus no use (hormone replacement therapy, statins, aspirin, and nonsteroidal anti-inflammatory medications), body mass index (< 25 [reference], 25 to 30, > 30 kg/m^2, missing), Charlson comorbidity score (≤ 1 [reference], 2 to 3, > 3), excessive alcohol use versus no use, smoking status (never [reference], ever, missing).

Table A4. Crude and Adjusted Hazard Ratios of Breast Cancer Associated With Use of Long-Acting Insulin Analogs Compared With Neutral Protamine Hagedorn Insulin Use Among New and Prior Insulin Users

Exposure	No. of Patients	No. of Breast Cancer Cases	Person-Years	Incidence Rate (95% CI)*	Hazard Ratios (95% CI)	
					Crude	Adjusted†
New insulin users						
NPH	2,652	34	11,743	2.9 (2.1 to 4.1)	1.00	1.00 (reference)
Glargine	4,148	67	20,170	3.3 (2.6 to 4.2)	1.13 (0.75 to 1.71)	1.18 (0.77 to 1.81)
Detemir	1,262	11	5,452	2.0 (1.1 to 3.6)	0.67 (0.34 to 1.33)	0.89 (0.42 to 1.88)
Prior insulin users‡						
NPH	6,897	74	23,334	3.2 (2.5 to 4.0)	1.00	1.00 (reference)
Glargine	5,427	109	28,515	3.8 (3.2 to 4.6)	1.24 (0.92 to 1.68)	1.53 (1.10 to 2.12)
Detemir	2,009	26	9,382	2.8 (1.9 to 4.1)	0.89 (0.57 to 1.39)	1.39 (0.83 to 2.31)

Abbreviation: NPH, neutral protamine Hagedorn.
*Per 1,000 person-years.
†The multivariable Cox proportional hazards model was adjusted for the following covariates before study cohort entry: age (years), calendar year, diabetes duration (years), prior duration of insulin use (years), hemoglobin A1c (< 6.5% [reference], 6.5% to 8.0%, > 8.0%, missing), use of antidiabetic medications versus no use (metformin, sulfonylureas, thiazolidinedione, and others), other medication use versus no use (hormone replacement therapy, statins, aspirin, and nonsteroidal anti-inflammatory medications), body mass index (< 25 [reference], 25 to 30, > 30 kg/m^2, missing), Charlson comorbidity score (≤ 1 [reference], 2 to 3, > 3), excessive alcohol use versus no use, smoking status (never [reference], ever, missing).
‡Prior insulin users were defined as women with at least any type of insulin before study cohort entry.

Table A5. Crude and Adjusted Hazard Ratios of Breast Cancer Associated With Cumulative Dose of Long-Acting Insulin Glargine Prescriptions Compared With Neutral Protamine Hagedorn Insulin in the Same Category Among New and Prior Insulin Users

Exposure, No. of Prescriptions	New Insulin Users						Prior Insulin Users‡					
	No. of Patients	No. of Breast Cancer Cases	PT	CIR (95% CI)*	Hazard Ratios (95% CI)		No. of Patients	No. of Breast Cancer Cases	PT	CIR (95% CI)*	Hazard Ratios (95% CI)	
					Crude	Adjusted†					Crude	Adjusted†
NPH (reference)												
10	2,652	15	4,927	3.0 (1.8 to 5.0)	1.00	1.00	6,897	45	11,209	4.0 (3.0 to 5.4)	1.00	1.00
10-30	1,685	12	3,671	3.3 (1.9 to 5.8)	1.00	1.00	3,448	21	7,634	2.8 (1.8 to 4.2)	1.00	1.00
30	890	7	3,144	2.2 (1.1 to 4.7)	1.00	1.00	1,403	8	4,491	1.8 (0.9 to 3.6)	1.00	1.00
Glargine												
10	4,148	37	8,938	4.1 (3.0 to 5.7)	1.42 (0.77 to 2.62)	1.34 (0.71 to 2.50)	5,427	36	10,933	3.3 (2.4 to 4.6)	0.81 (0.52 to 1.25)	0.97 (0.61 to 1.53)
10-30	2,645	20	6,652	3.0 (1.9 to 4.7)	0.95 (0.46 to 1.94)	0.98 (0.47 to 2.02)	3,737	41	10,473	3.9 (2.9 to 5.3)	1.46 (0.86 to 2.47)	1.83 (1.06 to 3.17)
30	1,298	10	4,580	2.2 (1.2 to 4.1)	0.99 (0.38 to 2.61)	1.11 (0.42 to 2.95)	1,958	32	7,109	4.5 (3.2 to 6.4)	2.58 (1.19 to 5.61)	3.24 (1.47 to 7.12)

Abbreviations: CIR, crude incidence rate; NPH, neutral protamine Hagedorn; PT, person-time.

*Per 1,000 person-years.

†The multivariable Cox proportional hazards model was adjusted for the following covariates before study cohort entry: age (years), calendar year, diabetes duration (years), prior duration of insulin use (years), hemoglobin A1c (< 6.5% [reference], 6.5% to 8.0%, > 8.0%, missing), use of antidiabetic medications versus no use (metformin, sulfonylureas, thiazolidinedione, and others), other medication use versus no use (hormone replacement therapy, statins, aspirin, and nonsteroidal anti-inflammatory medications), body mass index (< 25 [reference], 25 to 30, > 30 kg/m^2, missing), Charlson comorbidity score (≤ 1 [reference], 2 to 3, > 3), excessive alcohol use versus no use, smoking status (never [reference], ever, missing).

‡Prior insulin users were defined as women with at least any type of insulin before study cohort entry.