Similar Breast Cancer Risk in Women Older Than 65 Years Initiating Glargine, Detemir, and NPH Insulins

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Diabetes Care 2020;43:785–792 | https://doi.org/10.2337/dc19-0614

OBJECTIVE

To assess whether initiation of insulin glargine (glargine), compared with initiation of NPH or insulin detemir (detemir), was associated with an increased risk of breast cancer in women with diabetes.

RESEARCH DESIGN AND METHODS

This was a retrospective new-user cohort study of female Medicare beneficiaries aged ≥65 years initiating glargine (203,159), detemir (67,012), or NPH (47,388) from September 2006 to September 2015, with follow-up through May 2017. Weighted Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% CIs for incidence of breast cancer according to ever use, cumulative duration of use, cumulative dose of insulin, length of follow-up time, and a combination of dose and length of follow-up time.

RESULTS

Ever use of glargine was not associated with an increased risk of breast cancer compared with NPH (HR 0.97; 95% CI 0.88–1.06) or detemir (HR 0.98; 95% CI 0.92–1.05). No increased risk was seen with glargine use compared with either NPH or detemir by duration of insulin use, length of follow-up, or cumulative dose of insulin. No increased risk of breast cancer was observed in medium- or high-dose glargine users compared with low-dose users.

CONCLUSIONS

Overall, glargine use was not associated with an increased risk of breast cancer compared with NPH or detemir in female Medicare beneficiaries.

Long-acting insulin analogs, insulin glargine (glargine) and insulin detemir (detemir), are structurally altered human insulins designed to overcome the limitations of neutral protamine Hagedorn (NPH) insulin, namely, its short half-life and risk of nocturnal hypoglycemia. However, altering human insulin may influence mitogenicity, and so concern was raised about the carcinogenic potential of glargine. Indeed, in vitro studies showed that glargine had more potent mitogenic properties (up to eightfold) than regular insulin (1) and a substantially higher proliferative effect on breast cancer cells compared with other insulins (2). However, further studies suggested that in vivo metabolites of glargine, M1 and M2, were not mitogenic and are most measurable after insulin glargine administration with very little to none of the intact molecule (M0) detectable (3–5).

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Received 27 March 2019 and accepted 26 January 2020

This article contains Supplementary Data online at https://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-0614/-/DC1.

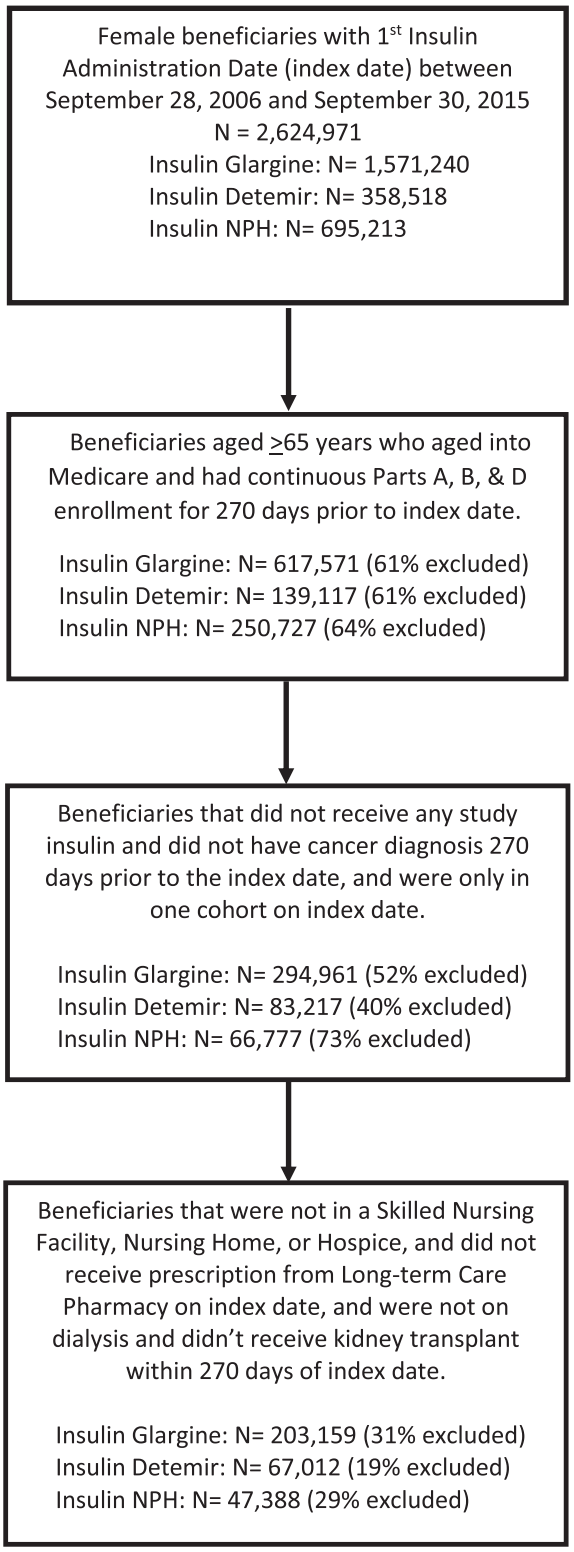

Figure 1—Study exclusions flowchart.

Due to concerns about carcinogenicity, several European observational studies examined the possibility of an association between glargine and cancer, although results were inconsistent (6–9). Since then, a study conducted at Kaiser Permanente Northern California (KPNC) reported an increased risk of breast cancer among glargine users who used the drug for ≥2 years compared with NPH (hazard ratio [HR] 1.6; 95% CI 1.1–2.4) (10). Another study, conducted using U.S. prescription claims data, reported no increased risk of breast, prostate, or colon cancer among patients initiating glargine compared with NPH (11).

A recent study in the Clinical Practice Research Datalink (CPRD) reported that compared with NPH use, long-term use of glargine (≥5 years) was associated with an increased risk of breast cancer, although this elevated risk was restricted to prior insulin users (HR 1.53; 95% CI 1.10–2.12) and was not seen in new initiators or in detemir users (12). This study represented an update on a previous study in the same database published in 2011, which reported similar findings with a significantly increased risk of breast cancer seen only among long-term users of glargine who were prior insulin users (HR 2.7; 95% CI 1.1–6.5) and not in new initiators (13).

The Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial, a multicenter international trial that examined cardiovascular and cancer outcomes in patients with dysglycemia assigned to glargine versus standard care, found no association between insulin glargine use and breast cancer (HR 1.01; 0.60–1.71) or any other cancer (14).

Given the inconsistent findings and small numbers of long-term glargine and detemir users in previous observational studies, uncertainty remains as to whether longer-term glargine use influences breast cancer risk. Additionally, insulin glargine is widely used in the U.S., accounts for 81.3% of the long-acting analog insulin prescription share (15), and was second from the top in terms of drug expenditures in 2017 (16). Therefore, we used Medicare data to assess whether long-term use of glargine, specifically, compared with use of NPH or detemir, was associated with an increased risk of breast cancer in women with diabetes.

RESEARCH DESIGN AND METHODS

Study Cohort

Female Medicare beneficiaries, aged ≥65 years, enrolled in fee-for-service Medicare Part A (hospitalization), Part B (office-based medical care), and Part D (prescription drugs) were eligible for study inclusion if they initiated a study insulin (glargine, detemir, or NPH) between

Table 1—Demographic and clinical characteristics of Medicare beneficiaries initiating glargine, detemir, or NPH from 2006 to 2015 after IPTW

	Insulin glargine and NPH cohort					Insulin glargine and insulin detemir cohort				
	Insulin glargine		NPH			Insulin glargine		Insulin detemir		
	n	%	*n*	%	SMD	*n*	%	*n*	%	SMD
Base population	203,159		205,672			203,159		202,436		
Characteristics										
Age (years)										
65–74	104,862	52	109,893	53	0.04	104,862	52	104,810	52	0.00
75–84	73,159	36	71,570	35	0.03	73,159	36	72,797	36	0.00
>85	25,138	12	24,210	12	0.02	25,138	12	24,828	12	0.00
Race										
White	153,258	75	157,618	77	0.03	153,258	75	152,926	76	0.00
Black	26,965	13	26,200	13	0.02	26,965	13	26,750	13	0.00
Other	22,936	11	21,854	11	0.02	22,936	11	22,760	11	0.00
Low income status										
Received LIS	88,965	44	86,528	42	0.03	88,965	44	88,341	44	0.00
No LIS	114,194	56	119,145	58	0.03	114,194	56	114,095	56	0.00
Zip code–level income										
<$30,000	40,883	20	40,685	20	0.01	40,883	20	40,535	20	0.00
$30,000 to $60,000	132,179	65	134,631	65	0.01	132,179	65	132,103	65	0.00
>$60,000	23,125	11	23,366	11	0.00	23,125	11	22,851	11	0.00
Unknown	6,972	3	6,990	3	0.00	6,972	3	6,946	3	0.00
Metropolitan statistical area										
Nonrural	150,546	74	152,153	74	0.00	150,546	74	149,473	74	0.01
Rural	52,613	26	53,519	26	0.00	52,613	26	52,963	26	0.01
Medication use										
ACE inhibitors/ARBs	150,737	74	151,630	74	0.01	150,737	74	150,133	74	0.00
Antiplatelets	35,793	18	36,943	18	0.01	35,793	18	35,525	18	0.00
β-Blockers	108,073	53	110,657	54	0.01	108,073	53	107,485	53	0.00
Calcium channel blockers	81,775	40	83,265	40	0.00	81,775	40	81,276	40	0.00
Digoxin	15,565	8	16,449	8	0.01	15,565	8	15,410	8	0.00
Diuretics, loop	74,931	37	77,695	38	0.02	74,931	37	74,331	37	0.00
Diuretics, potassium	20,611	10	21,510	10	0.01	20,611	10	20,623	10	0.00
Diuretics, thiazides	75,135	37	75,393	37	0.01	75,135	37	74,909	37	0.00
Fibrates	16,710	8	17,189	8	0.00	16,710	8	16,805	8	0.00
SSRI antidepressants	41,996	21	43,597	21	0.01	41,996	21	41,777	21	0.00
Diabetes drugs	183,422	90	186,421	91	0.01	183,422	90	182,752	90	0.00
Metformin	109,848	54	110,897	54	0.00	109,848	54	109,647	54	0.00
Sulfonylureas	109,428	54	112,946	55	0.02	109,428	54	109,240	54	0.00
Thiazolidinediones	35,959	18	36,263	18	0.00	35,959	18	35,532	18	0.00
Nonstudy insulins	53,288	26	56,493	27	0.03	53,288	26	53,042	26	0.00
Other antidiabetes drugs	53,504	26	55,364	27	0.01	53,504	26	53,609	26	0.00
Statins	135,854	67	137,108	67	0.00	135,854	67	135,475	67	0.00
Hormone replacement therapy	7,751	4	8,293	4	0.01	7,751	4	7,711	4	0.00
Medical conditions										
Heart failure	54,182	27	57,395	28	0.03	54,182	27	53,618	26	0.00
Hypertension	186,644	92	189,144	92	0.00	186,644	92	186,116	92	0.00
COPD	37,974	19	40,098	19	0.02	37,974	19	37,791	19	0.00
aDCSI score (categorical)										
0	42,287	21	41,066	20	0.02	42,287	21	42,336	21	0.00
1–2	69,298	34	69,223	34	0.01	69,298	34	68,897	34	0.00
3–4	52,482	26	53,803	26	0.01	52,482	26	52,378	26	0.00
≥5	39,092	19	41,580	20	0.02	39,092	19	38,824	19	0.00
Charlson Comorbidity Index (categorical)										
0	129,403	64	124,790	61	0.06	129,403	64	129,380	64	0.00
1–2	32,669	16	35,355	17	0.03	32,669	16	32,290	16	0.00
3–4	24,738	12	27,462	13	0.04	24,738	12	24,511	12	0.00
≥5	16,349	8	18,066	9	0.03	16,349	8	16,255	8	0.00
Obesity	35,963	18	37,382	18	0.01	35,963	18	36,376	18	0.01
Chronic kidney failure	52,611	26	55,764	27	0.03	52,611	26	52,402	26	0.00
Acute kidney failure	26,175	13	29,676	14	0.04	26,175	13	26,016	13	0.00
Alcohol abuse	1,398	1	1,568	1	0.01	1,398	1	1,400	1	0.00
Smoking	19,044	9	20,837	10	0.03	19,044	9	19,155	9	0.00

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Table 1—Continued

	Insulin glargine and NPH cohort					Insulin glargine and insulin detemir cohort				
	Insulin glargine		NPH			Insulin glargine		Insulin detemir		
	n	%	*n*	%	SMD	*n*	%	*n*	%	SMD
Health care utilization										
Hospitalizations										
0	128,248	63	123,559	60	0.06	128,248	63	128,275	63	0.00
1	43,385	21	46,163	22	0.03	43,385	21	42,946	21	0.00
2	17,868	9	19,955	10	0.03	17,868	9	17,774	9	0.00
≥3	13,658	7	15,995	8	0.04	13,658	7	13,441	7	0.00
ER visits										
0	141,159	69	139,990	68	0.03	141,159	69	140,860	70	0.00
1	40,573	20	42,643	21	0.02	40,573	20	40,301	20	0.00
2	12,898	6	13,787	7	0.01	12,898	6	12,798	6	0.00
≥3	8,529	4	9,251	4	0.01	8,529	4	8,477	4	0.00
Physician visits										
0	8,097	4	8,242	4	0.00	8,097	4	7,843	4	0.01
1–4	27,845	14	27,375	13	0.01	27,845	14	27,583	14	0.00
5–10	52,475	26	52,350	25	0.01	52,475	26	52,155	26	0.00
11–20	63,618	31	64,725	31	0.00	63,618	31	63,672	31	0.00
21–30	29,351	14	30,678	15	0.01	29,351	14	29,393	15	0.00
≥31	21,773	11	22,302	11	0.00	21,773	11	21,790	11	0.00
Mammogram screening	45,521	22	46,765	23	0.01	45,521	22	45,602	23	0.00
Physician specialty										
Endocrinology	19,628	10	23,599	11	0.06	19,628	10	19,847	10	0.00
Primary care	108,002	53	105,783	51	0.03	108,002	53	108,426	54	0.01
Other	75,529	37	76,291	37	0.00	75,529	37	74,163	37	0.01

ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; ER, emergency room; LIS, low income subsidy; SMD, standardized mean difference; SSRI, selective serotonin reuptake inhibitor.

September 2006 and September 2015 and if in the 270 days prior to the date of the qualifying prescription (index date) they had continuous enrollment in Medicare, had no prior cancer diagnosis, and did not receive a prescription for a study insulin. Patients were excluded if they were in a skilled nursing facility or nursing home or if they received the index prescription from a long-term care pharmacy or were receiving hospice care on the index date. Kidney transplant recipients, patients undergoing dialysis, and anyone who entered Medicare for reasons other than age were also excluded (Fig. 1).

Exposure

The primary exposure definition was ever use of glargine, detemir, or NPH. Duration of insulin use, defined as cumulative days' supply in years (0 to <3, 3 to <5, and ≥5), and insulin dose, defined as cumulative units of insulin dispensed (0–20,000, 20,000–60,000, and ≥60,000), were also examined, as was length of follow-up time in years (0 to <3, 3 to <5, and ≥5). In addition, dose in combination with duration of follow-up (e.g., 0 to <3 years and 0 to <20,000 units) was investigated.

Follow-up

An intention-to-treat approach to follow-up time was applied in our primary analyses. Follow-up began the day after cohort entry (index date) and continued until one of the following: death, disenrollment from Medicare, end of study (31 May 2017), switching to other study insulin, switching to insulin degludec, or diagnosis of breast cancer.

Outcomes

Breast cancer was identified using a previously validated algorithm developed by Setoguchi et al. (17). Breast cancer case subjects were defined as those who had two or more diagnoses of breast cancer recorded within 2 months. The date of the second breast cancer diagnosis was used as the outcome date. This definition resulted in high specificity (99.62%) and a good PPV (76.56%) in the validation study.

Baseline Covariates

Preexisting medical conditions, medication use, an adapted Diabetes Complications Severity Index (aDCSI) (18), and health care utilization covariates were identified in the 9-month baseline period prior to cohort entry. Logistic regression was used to estimate the probability of receiving glargine versus NPH and glargine versus detemir and to further calculate inverse probability of treatment weights (IPTW). Average treatment effects among treated (ATT) IPTW weights, with glargine considered the reference treatment, were applied. The distributions of propensity scores and ATT IPTW were inspected for outliers. Weight truncation at the 99th percentile was conducted for extreme weights in the detemir and NPH cohorts. Covariate balance between the weighted cohorts was assessed using standardized mean differences, with a value ≤0.1 indicating a negligible difference between groups (19).

Statistical Analysis

All analyses were based on IPTW-adjusted cohorts and therefore accounted for potential confounding by baseline factors. Crude breast cancer incidence rates per 1,000 person-years (PY) and 95% CIs were calculated from standard (unweighted) Cox proportional hazards models. Weighted Cox proportional hazards regression with robust SEs was used to estimate weight-adjusted HRs and 95% CIs for incidence of breast cancer among glargine users

Table 2—Crude incidence rates and adjusted HR for breast cancer risk among glargine users compared with NPH users, by ever use, duration of use, cumulative dose, and length of follow-up

	Users	Breast cancers	PY of follow-up	Crude breast cancer incidence rate per 1,000 PY (95% CI)	Unweighted HR (95% CI)	Weighted HR (95% CI)
Ever use						
Glargine	203,159	4,170	691,342	6.03 (5.85–6.21)	1.00 (0.93–1.08)	0.97 (0.88–1.06)
NPH	47,388	864	143,628	6.02 (5.61–6.42)	Ref	Ref
Duration of use (years)						
Glargine 0 to <3	203,159	3,675	612,556	6.00 (5.81–6.19)	0.98 (0.91–1.06)	0.96 (0.87–1.06)
NPH 0 to <3	47,388	793	129,464	6.13 (5.70–6.55)	Ref	Ref
Glargine 3 to <5	37,143	392	61,592	6.36 (5.73–6.99)	1.33 (0.99–1.77)	1.11 (0.76–1.62)
NPH 3 to <5	5,694	52	10,798	4.82 (3.51–6.12)	Ref	Ref
Glargine ≥5	10,875	103	17,194	5.99 (4.83–7.15)	1.06 (0.65–1.74)	0.68 (0.37–1.24)
NPH ≥5	1,847	19	3,365	5.65 (3.11–8.18)	Ref	Ref
Cumulative dose (units)						
Glargine 0 to <20,000	203,159	2,835	475,080	5.97 (5.75–6.19)	0.98 (0.89–1.07)	0.96 (0.86–1.08)
NPH 0 to <20,000	47,388	574	93,994	6.11 (5.61–6.61)	Ref	Ref
Glargine 20,000 to <60,000	79,494	1,014	169,817	5.97 (5.60–6.34)	1.06 (0.91–1.24)	0.99 (0.81–1.22)
NPH 20,000 to <60,000	16,663	198	34,029	5.82 (5.01–6.63)	Ref	Ref
Glargine ≥60,000	21,318	321	46,446	6.91 (6.16–7.67)	1.29 (1.02–1.63)	1.14 (0.83–1.56)
NPH ≥60,000	5,924	92	15,605	5.90 (4.69–7.10)	Ref	Ref
Length of follow-up (years)						
Glargine 0 to <3	203,159	2,780	447,539	6.21 (5.98–6.44)	0.96 (0.88–1.05)	0.95 (0.85–1.06)
NPH 0 to <3	47,388	603	93,519	6.45 (5.93–6.96)	Ref	Ref
Glargine 3 to <5	98,328	840	143,568	5.85 (5.46–6.25)	1.08 (0.91–1.28)	1.03 (0.83–1.28)
NPH 3 to <5	19,150	154	28,381	5.43 (4.57–6.28)	Ref	Ref
Glargine ≥5	49,515	550	100,235	5.49 (5.03–5.95)	1.11 (0.90–1.37)	0.97 (0.74–1.26)
NPH ≥5	10,136	107	21,728	4.92 (3.99–5.86)	Ref	Ref

Data are *n* unless otherwise indicated. Ref, reference.

compared with users of NPH and detemir. As there were no significant differences in observed confounders across cohorts after the weighting, the weighted Cox model included a treatment indicator as a sole covariate leading to estimation of the marginal treatment effect on the breast cancer risk. Separate weighted Cox proportional hazards models were used to examine ever use, cumulative duration of use, cumulative dose of insulin, length of follow-up time, and a combination of cumulative dose and length of follow-up.

Secondary analyses were restricted to insulin users with ≥5 years of follow-up time. Within each insulin cohort, we compared women with low cumulative dose with those with medium or high cumulative dose for the occurrence of breast cancer.

A prespecified sensitivity analysis repeated the primary analyses using untruncated ATT IPTW weights.

This study was classified as public health surveillance by the U.S. Food and Drug Administration (FDA) and was exempted from review by the FDA's Research in Human Subjects Committee in accordance with the updated Common Rule. Analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC) and R 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 203,159 glargine, 67,012 detemir, and 47,388 NPH initiators contributed 691,342, 198,731, and 143,628 PY of follow-up, respectively. The median follow-up time in years for glargine, detemir, and NPH was 2.9 (interquartile range 1.44–4.93), 2.48 (1.22–4.21), and 2.32 (0.93–4.51), respectively. A median of four prescriptions per year was received by women in each of the insulin cohorts.

Before IPTW adjustment, there were minor differences in clinical characteristics between the glargine and detemir cohorts related to diabetes medications, comorbidity score, hospitalizations, and physician specialty. Differences in demographics and clinical characteristics between NPH and glargine cohorts were more frequent and substantial than those between glargine and detemir cohorts and included race, income level, use of statins and diabetes drugs, numbers of physician visits, and physician specialty (Supplementary Table 1). After IPTW adjustment, all cohorts were closely balanced for all covariates (Table 1).

During up to 10.7 years of follow-up, there were 6,267 breast cancers identified: 4,170 (66%) in glargine initiators, 864 (14%) in NPH initiators, and 1,233 (20%) in detemir initiators. The crude breast cancer incidence rates per 1,000 PY were similar across the insulin cohorts, ranging from 6.02 to 6.20 (Tables 2 and 3).

Ever use of glargine was not associated with an increased risk of breast cancer compared with NPH (HR 0.97; 95% CI 0.88–1.06) or detemir (HR 0.98; 95% CI 0.92–1.05). No increased risk was seen with glargine use compared with either NPH or detemir when stratifying by duration of insulin use, by length of follow-up, or by cumulative dose of insulin dispensed (Tables 2 and 3 and Supplementary Fig. 1).

On examination of both cumulative dose and length of follow-up combined, no increased risk of breast cancer was found among glargine users compared with NPH or detemir users, except among those using insulin for 3–5 years and with a cumulative dose of ≥60,000 units. An HR

Table 3—Crude incidence rates and adjusted HR for breast cancer among glargine users compared with detemir users by ever use, duration of use, cumulative dose, and length of follow-up

	Users	Breast cancers	PY of follow-up	Crude breast cancer incidence rate per 1,000 PY (95% CI)	Unweighted HR (95% CI)	Weighted HR (95% CI)
Ever use						
Glargine	203,159	4,170	691,342	6.03 (5.85–6.21)	0.98 (0.92, 1.04)	0.98 (0.92,1.05)
Detemir	67,012	1,233	198,731	6.20 (5.86–6.55)	Ref	Ref
Duration of use (years)						
Glargine 0 to <3	203,159	3,675	612,556	6.00 (5.81–6.19)	0.97 (0.90, 1.03)	0.97 (0.90, 1.04)
Detemir 0 to <3	67,012	1,122	179,875	6.24 (5.87–6.60)	Ref	Ref
Glargine 3 to <5	37,143	392	61,592	6.36 (5.73–6.99)	1.14 (0.90, 1.44)	1.14 (0.90, 1.46)
Detemir 3 to <5	9,872	87	15,317	5.68 (4.49–6.87)	Ref	Ref
Glargine ≥5	10,875	103	17,194	5.99 (4.83–7.15)	0.89 (0.57, 1.38)	0.91 (0.57, 1.43)
Detemir ≥5	2,510	24	3,539	6.78 (4.07–9.50)	Ref	Ref
Cumulative dose (units)						
Glargine 0 to <20,000	203,159	2,835	475,080	5.97 (5.75–6.19)	0.96 (0.89, 1.04)	0.97 (0.90–1.05)
Detemir 0 to <20,000	67,012	882	141,663	6.23 (5.82–6.64)	Ref	Ref
Glargine 20,000 to <60,000	79,494	1,014	169,817	5.97 (5.60–6.34)	1.00 (0.87, 1.14)	0.98 (0.85–1.13)
Detemir 20,000 to <60,000	23,557	266	43,509	6.11 (5.38–6.85)	Ref	Ref
Glargine ≥60,000	21,318	321	46,446	6.91 (6.16–7.67)	1.13 (0.89, 1.45)	1.12 (0.87–1.44)
Detemir ≥60,000	6,535	85	13,558	6.27 (4.94–7.60)	Ref	Ref
Length of follow-up (years)						
Glargine 0 to <3	203,159	2,780	447,539	6.21 (5.98–6.44)	1.00 (0.92, 1.08)	1.00 (0.93, 1.08)
Detemir 0 to <3	67,012	871	139,729	6.23 (5.82–6.65)	Ref	Ref
Glargine 3 to <5	98,328	840	143,568	5.85 (5.46–6.25)	0.96 (0.83, 1.11)	0.96 (0.82, 1.11)
Detemir 3 to <5	27,473	228	37,532	6.07 (5.29–6.86)	Ref	Ref
Glargine ≥5	49,515	550	100,235	5.49 (5.03–5.95)	0.88 (0.73, 1.07)	0.90 (0.74, 1.09)
Detemir ≥5	11,891	134	21,469	6.24 (5.18–7.30)	Ref	Ref

Data are *n* unless otherwise indicated. Ref, reference.

of 1.62 (95% CI 1.02–2.58) was observed for glargine versus NPH, and an HR 1.53 (95% CI 0.99–2.36) was observed for glargine versus detemir. Despite this, among those with the longest follow-up time and highest cumulative doses of glargine combined (≥5 years and ≥60,000 units), there was no difference in breast cancer risk for glargine versus NPH (HR 0.99; 95% CI 0.63–1.57) or for glargine versus detemir (HR 0.89; 95% CI 0.65–1.21) (Table 4, Supplementary Table 2, and Supplementary Fig. 1).

Among patients with ≥5 years of follow-up, there was no difference in breast cancer risk at different cumulative doses of glargine or detemir. For NPH, risk was reduced in patients with intermediate but not high cumulative exposure (Supplementary Table 3). The results of the sensitivity analysis using untruncated weights were consistent with those from the main analysis (data not shown).

CONCLUSIONS

In this large new-user, active comparator, cohort study, which included almost 320,000 insulin initiators, no association was seen between ever use of glargine and breast cancer risk, compared with use of NPH or detemir. This null association persisted across levels of dose, duration of use, and length of follow-up. There was also no increased risk of breast cancer observed in those who had ≥5 years of follow-up and who used medium- or high-dose glargine compared with low-dose users.

These results conflict with those of a recent study by Wu et al. (12), which reported that compared with NPH, glargine use was associated with an increased risk of breast cancer (HR 1.44; 95% CI 1.11–1.85), especially after 5 years of use (HR 2.23; 95% CI 1.32–3.77) and with ≥30 prescriptions (HR 2.29; 95% CI 1.26–4.16). However, these differences are likely the result of differences in study design, population size, and potential imbalances in the cohorts studied. First, the primary results of Wu et al. were derived from the entire cohort of insulin initiators, using a prevalent new-user design, which has been proposed as a way of including in a study new initiators of a drug who have also used the older comparator drug and so are not treatment naïve to both study drugs (20). Prevalent new-user designs, though, may be limited by selection bias, immortal time bias, and issues with properly timing covariates in the baseline period. When the analysis by Wu et al. was restricted to new users only, as we did in our study, no increased risks were seen for ever use of glargine compared with NPH (HR 1.18; 95% CI 0.77–1.81) or with ≥5 years of use (HR 1.60; 95% CI 0.66–3.84). The association between glargine and breast cancer seemed to be particularly concentrated among prior insulin users (HR 1.53; 95% CI 1.10–2.12). Second, there were just 4,148 new glargine users in that study compared with our 203,159 glargine initiators, increasing confidence in our estimates. Third, in the study by Wu et al., the breast cancer incidence rate per 1,000 person-years decreased among NPH users as duration of use increased, from 3.6 (95% CI 2.8–4.5) in those with <3 years' exposure to 2.2 (95% CI 1.4–3.5) for those with ≥5 years' exposure, while in glargine users it increased slightly. The decreased breast cancer incidence in longer-term users of NPH may have contributed to a potentially spurious increased HR for glargine users. NPH users tended to be

Table 4—Crude incidence rates and adjusted HR for breast cancer among glargine users compared with NPH users according to duration of use and cumulative dose of insulin use combined

Duration of use; cumulative dose of insulin combined (units)	Users	Breast cancers	PY of follow-up	Crude breast cancer incidence rate per 1,000 PY (95% CI)	Unweighted HR (95% CI)	Weighted HR (95% CI)
Glargine 0 to <3 years; 0 to <20,000	203,159	2,394	388,400	6.16 (5.92–6.41)	0.98 (0.88–1.08)	0.97 (0.85–1.10)
NPH 0 to <3 years; 0 to <20,000	47,388	472	74,431	6.34 (5.77–6.91)	Ref	Ref
Glargine 3 to <5 years; 0 to <20,000	52,689	307	60,143	5.10 (4.53–5.68)	1.12 (0.84–1.49)	1.07 (0.74–1.56)
NPH 3 to <5 years; 0 to <20,000	9,238	55	12,003	4.58 (3.37–5.79)	Ref	Ref
Glargine ≥5 years; 0 to <20,000	15,667	134	26,537	5.05 (4.19–5.90)	0.81 (0.58–1.12)	0.75 (0.50–1.10)
NPH ≥5 years; 0 to <20,000	3,763	47	7,561	6.22 (4.44–7.99)	Ref	Ref
Glargine 0 to <3 years; 20,000 to <60,000	60,817	368	57,096	6.45 (5.79–7.10)	1.03 (0.82–1.29)	1.00 (0.75–1.34)
NPH 0 to <3 years; 20,000 to <60,000	14,974	109	16,934	6.44 (5.23–7.65)	Ref	Ref
Glargine 3 to <5 years; 20,000 to <60,000	58,132	425	70,540	6.02 (5.45–6.60)	0.96 (0.75–1.24)	0.88 (0.63–1.21)
NPH 3 to <5 years; 20,000 to <60,000	9,056	68	10,864	6.26 (4.77–7.75)	Ref	Ref
Glargine ≥5 years; 20,000 to <60,000	27,753	221	42,181	5.24 (4.55–5.93)	1.55 (0.99–2.42)	1.34 (0.72–2.49)
NPH ≥5 years; 20,000 to <60,000	3,790	21	6,231	3.37 (1.93–4.81)	Ref	Ref
Glargine 0 to <3 years; ≥60,000	3,782	18	2,043	8.81 (4.74–12.88)	0.93 (0.51–1.71)	0.77 (0.38–1.58)
NPH 0 to <3 years; ≥60,000	2,834	22	2,154	10.21 (5.94–14.48)	Ref	Ref
Glargine 3 to <5 years; ≥60,000	13,064	108	12,885	8.38 (6.80–9.96)	1.49 (0.99–2.23)	1.62 (1.02–2.58)
NPH 3 to <5 years; ≥60,000	4,411	31	5,513	5.62 (3.64–7.60)	Ref	Ref
Glargine ≥5 years; ≥60,000	16,665	195	31,517	6.19 (5.32–7.06)	1.26 (0.89–1.78)	0.99 (0.63–1.57)
NPH ≥5 years; ≥60,000	3,804	39	7,937	4.91 (3.37–6.46)	Ref	Ref

Data are *n* unless otherwise indicated. Ref, reference.

older than glargine users (mean age 70 years vs. 64 years, respectively) and so were less likely to get screened for breast cancer according to U.K. National Health Service breast screening guidelines (21), which may explain the lower incidence of breast cancer in these users across time.

A retrospective cohort study conducted in the Inovalon Medical Outcomes Research for Effectiveness and Economics Registry (MORE^2) registry by Stürmer et al. (11), which used claims data similar to those used in our study, also found no association between glargine use and breast cancer risk (HR for ever use of glargine compared with NPH was 1.07 [95% CI 0.65–1.75] and for duration ≥2 years was 0.67 [95% CI 0.18–2.54]).

While the findings were similar, our study was larger than the study by Sturmer et al. (11), with 203,159 glargine and 47,388 NPH initiators compared with 43,306 glargine initiators and 9,147 NPH initiators, and had longer median durations of follow-up: 2.9 in the glargine cohort and 2.3 in the NPH cohort compared with 0.9 and 0.8, respectively. We also conducted detailed analyses on dose of glargine used and dose and duration of use combined.

A meta-analysis of seven cohort studies, published in 2012, also found no difference in breast cancer incidence rates in glargine users compared with users of other types of insulin, although considerable heterogeneity (I^2 = 74%) was seen across the included studies, which may have influenced the summary estimate (22).

Our findings are also similar those of the ORIGIN trial, which reported no association between insulin glargine use and breast cancer compared with standard care. However, that trial had only 56 breast cancer cases (28 in each arm), while our study included 6,267 breast cancers with 4,170 (66%) occurring in glargine initiators, 864 (14%) in NPH initiators, and 1,233 (20%) in detemir initiators.

We did not find any evidence of increased breast cancer risk in glargine users in analyses examining ever use, dose, duration of use, and length of follow-up individually; however, in our analysis that examined length of follow-up and dose simultaneously, an increased risk of breast cancer was seen in glargine users compared with NPH who used high-dose insulin, ≥60,000 units, over a relatively short period of time (3–5 years' follow-up). Despite this finding, there was no increased risk seen among those using high-dose insulin across either shorter or longer time periods (0–3 years or ≥5 years of follow-up) and so this may be due to chance given the large number of analyses conducted. As a post hoc analysis, at the request of a reviewer, we conducted an adjustment for multiple comparisons in our primary analyses for each of our cohort comparisons (glargine vs. NPH and glargine vs. detemir) using the Benjamini-Hochberg procedure. No statistically significant results were found after the adjustment. Specifically, in the analysis of both cumulative dose and length of follow-up combined among those with 3–5 years of follow-up and ≥60,000 units, the Q value from the adjustment was 0.81, suggesting that our finding of an increased risk of breast cancer in this category was due to chance. A numerically increased risk was also seen in analyses comparing glargine and detemir, among those using high-dose insulin over a relatively short period of time (3–5 years of follow-up and 1–3 years of follow-up), although statistical significance was not achieved and there was no suggestion of increased risk in the period of ≥5 years of follow-up.

Our study has several strengths. First, it is the largest study to date to examine the association between glargine use and breast cancer risk and had almost five times as many glargine users as the next-largest

study that examined this question. Up to 10.7 years of follow-up time was available, with ~20% of all users having >5 years of follow-up. A new-user design was applied, rather than the prevalent new-user design used in some other studies, to avoid missing potential early effects of drugs and to accurately account for baseline confounders. An active comparator was used to reduce unmeasured confounding, and this was the first study to use detemir, also a long-acting analog insulin, in addition to NPH, as an active comparator for glargine. Our study was also the first study to date that examined insulin dose according to units of insulin dispensed rather than counting of numbers of prescriptions and the first that assessed the influence of cumulative dose and follow-up time combined. Unlike some previous studies, that used a multivariate adjustment approach to estimate risks, conditioning on confounders, our study used a propensity score method to estimate marginal risks across cohorts that correspond with the effect measures from randomized trials.

Our study did have some limitations. It was observational and therefore may be subject to confounding by factors not adjusted for in the analysis. The study population was aged ≥65 years, and so the generalizability of findings to those outside that age range may be limited. The Medicare claims data used in this study are ideal for capturing drug exposure but may be limited in identifying cancer diagnoses and potentially important covariates such as BMI and smoking. To address this, we used a validated algorithm (17) that has been applied in previous study of insulin glargine and cancer risk (11) that used claims data. That study, by Stürmer et al. (11), used two external validation studies to assess the potential for unmeasured confounding by BMI and showed that BMI did not affect the decision to initiate insulin treatment with glargine versus NPH. We also used ICD-9, National Drug Code, and Healthcare Common Procedure Coding System to identify, as much as possible, evidence of smoking and smoking status in the claims data. Diabetes has been associated with a slightly increased risk of breast cancer. A recent meta-analysis of 18 studies reported a summary relative risk of 1.13 (95% CI 1.04–1.24) (23). While we did not have information on diabetes duration, we did estimate a modified diabetes severity index and included it in the propensity score model to account for any potential confounding by diabetes severity.

In summary, insulin glargine use was not associated with an increased risk of breast cancer compared with NPH or detemir use, in female Medicare beneficiaries with diabetes, irrespective of dose, duration of use, or length of follow-up.

Funding. This study was funded by the FDA through an interagency agreement with the Centers for Medicare & Medicaid Services.

The views expressed in this manuscript are those of the authors and do not necessarily reflect the views of the FDA.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. M.C.B. designed the study, interpreted the results, and wrote and edited the manuscript. H.L., P.B., M.S., J.A.K., and D.J.G. designed the study, interpreted the results, and reviewed and edited the manuscript. Y.C., X.W., S.P., M.W., and T.E.M. designed the study, analyzed the data, and reviewed and edited the manuscript. M.C.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 34th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Prague, Czech Republic, 22–26 August 2018.

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