Cohort Study of Insulin Glargine and Risk of Breast, Prostate, and Colorectal Cancer Among Patients With Diabetes

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OBJECTIVE—To examine whether use of insulin glargine, compared with another long-acting insulin, is associated with risk of breast, prostate, colorectal cancer, or all cancers combined.

RESEARCH DESIGN AND METHODS—Computerized health records from Kaiser Permanente Northern and Southern California regions starting in 2001 and ending in 2009 were used to conduct a population-based cohort study among patients with diabetes aged ≥18 years. With use of Cox regression modeling, cancer risk in users of insulin glargine (n = 27,418) was compared with cancer risk in users of NPH (n = 100,757).

RESULTS—The cohort had a median follow-up of 3.3 years during which there was a median of 1.2 years of glargine use and 1.4 years of NPH use. Among users of NPH at baseline, there was no clear increase in risk of breast, prostate, colorectal, or all cancers combined associated with switching to glargine. Among those initiating insulin, ever use or ≥2 years of glargine was not associated with increased risk of prostate or colorectal cancer or all cancers combined. Among initiators, the hazard ratio (HR) for breast cancer associated with ever use of glargine was 1.3 (95% CI 1.0–1.8); the HR for breast cancer associated with use of glargine for ≥2 years was 1.6 or 1.7 depending on whether glargine users had also used NPH.

CONCLUSIONS—Results of this study should be viewed cautiously, given the relatively short duration of glargine use to date and the large number of potential associations examined.

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Although findings were not consistent, results of four observational studies conducted in Europe and reported in June 2009 raised concerns that use of the long-acting insulin analog, glargine (Lantus), may increase the risk of one or more forms of cancer (1–4). Insulin analogs are structurally altered human insulins. Because altering human insulin molecules may also alter mitogenicity, there was concern about the carcinogenic potential of glargine. Each of the four studies was conducted among patients with diabetes and used data from electronic records. The number of end points, especially for cancer at specific sites, was small; the period of observation was short; and data were not consistently complete or available on several potentially important confounding variables.

Subsequently, Sanofi, the manufacturer of glargine, supported the current study among Kaiser Permanente members to examine the potential association between use of insulin glargine and risk of breast, prostate, colorectal cancer, or all cancers combined. The final version of the full protocol for this study was submitted to the European Medicines Agency Committee for Medicinal Products for Human Use in March 2010. It was approved by the Committee for Medicinal Products for Human Use in April 2010.

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RESEARCH DESIGN AND METHODS

Setting and source population

The study was conducted among enrollees of Kaiser Permanente's Northern and Southern California regions (KPNC and KPSC). Together, these regions currently serve ~4.8 million adult members. Kaiser Permanente is a nonprofit, prepaid health plan. KPNC and KPSC own and run their hospitals and clinics, employ their own physicians, manage their own pharmacies, and archive data generated from clinical encounters.

Study cohort

The cohort included members 18 years old or older diagnosed with type 1 or type 2 diabetes identified from pharmacy records (fills for diabetes drugs), laboratory results (HbA_{1c} levels), and outpatient, emergency room, and hospitalization records listing a diagnosis of diabetes. The cohort was restricted to patients with no history of cancer.

Primary exposures of interest

The primary exposure of interest was insulin glargine. The comparator was human NPH (including NPH premixed with regular insulin), which is an intermediate-acting insulin with indications for use similar to those with glargine. Information on medication use came from computerized outpatient pharmacy records. Records include dispense date and drug name, amount, and days supply.

Eligible cohort members were categorized as "ever users" of glargine or NPH if they filled at least two prescriptions for the specific drug within a 6-month period. Estimating cumulative duration of insulin use from prescription data is difficult because of problems with adherence and wastage. Thus, duration was calculated in two ways. For our main analyses, we added the days between prescriptions; if days between two prescriptions was >6 months, then the days counted for the

earlier prescription was limited to 183. In sensitivity analyses, we summed the number of days supply for each prescription.

Outcomes of interest

The three primary outcomes included female breast, prostate, and colorectal cancer. The secondary outcome was all cancers combined, excluding nonmelanoma skin cancers.

Incident cancers through 31 December 2009 were identified by linkage with the KPNC and KPSC cancer registries, both of which are contributing sites to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program of cancer registries. The registries follow SEER practices and have comparable accuracy and completeness insured by standardized medical record abstraction.

Potential confounding variables

Electronic health records provided information on other diabetes medications and on demographics, laboratory tests (e.g., HbA_{1c}), BMI, and inpatient and outpatient diagnoses. For some variables (e.g., race/ethnicity, BMI), data from the electronic record were supplemented with information obtained from prior surveys conducted on subsets of the study cohort.

Cohort entry and follow-up (time at risk)

Entry into the cohort occurred on May 2001 (when glargine became available in the U.S.), or later, when the following inclusion criteria were met: at least 12 months of continuous health plan membership and pharmacy benefits, 18 years of age or older, and at least two prescriptions for insulin glargine or for NPH insulin within a 6-month period. For the main analyses, follow-up ended at diagnosis of any cancer, death, a gap of >4 months in either membership or prescription benefits, or 31 December 2009—whichever came first.

Statistical analyses

Analyses were conducted using multivariable Cox or Poisson regression modeling. Use of insulins and other diabetes medications was treated as time-varying covariates in regression models. Analyses were adjusted for potential confounders, including demographic and clinical variables. Sensitivity analyses examining various sets of additional potential confounders obtained via questionnaire were conducted in subsets of the study cohort.

RESULTS—The final eligible cohort included 115,514 adult men and women with diabetes (Supplementary Fig. 1). At the end of follow-up, there were 27,418 patients who had used insulin glargine and 100,757 who had used NPH (12,661 individuals had used both). Among new users of insulin (i.e., no use of any insulin in the prior 12 months), there were 6,548 whose first insulin was glargine—or ~25% of all glargine users. There were 39,708 new users of NPH—or ~40% of all NPH users.

As expected, there was a marked increase in use of glargine over time (Table 1). In the full cohort, age at first eligible glargine prescription was slightly younger than age at first eligible NPH fill. In contrast, the age distribution was similar in the new insulin users. In both the full cohort and new insulin users, users of glargine were more frequently male. There were only minimal racial/ethnic differences by insulin type. The proportion of NPH users without a documented BMI was substantially higher than for glargine users. Note, this is largely because we only included BMI measures within 24 months of first eligible prescription and a large proportion of first eligible NPH fills occurred prior to 2007, when the BMI began to be systematically calculated and recorded in the electronic medical records. When we restricted comparisons to persons with known BMI, the differences were reduced and the BMI distribution was similar among new insulin users. The proportion of adults with low income, based on median household income of their residence census track, was similar for glargine and NPH users. When we restricted to those with known smoking status, NPH users were more frequently current smokers.

Among the full cohort, the proportion using NPH in the 12 months prior to their first eligible glargine prescription after entry into the cohort was similar to the proportion using NPH prior to first eligible NPH after entry (Table 1). Use of short-acting insulin was more common and metformin and sulfonylurea use were less common in the 12 months prior to first eligible glargine prescription than at the first eligible NPH prescription. Among new users of insulin, the use of other diabetes medications was generally similar in the 12 months prior to first eligible glargine or NPH prescription. Use of thiazolidinediones, however, was more common among the new glargine users.

In the full cohort, there was a median of 3.3 years of follow-up (maximum 8.6). From the first eligible prescription for glargine to end of follow-up was a median of 2.3 years vs. a median of 3.6 years for NPH (Supplementary Table 1). In general, insulin users received glargine or NPH for only a portion of their follow-up period. There was a median of 1.2 years of glargine use and 1.4 years of NPH use (Supplementary Table 2).

There were 5,851 cohort members with at least one cancer diagnosed during follow-up: 910 with breast cancer, 753 with prostate cancer, and 700 with colorectal cancer. Among new insulin users, there were 269 with breast cancer, 253 with prostate cancer, 205 with colorectal cancer, and a total of 1,856 with cancer at any site. Cancer incidence rates were consistent with those reported for California by SEER and expected rates based on the reported association between diabetes and cancer (5) (Supplementary Table 3).

Given that NPH was our primary comparator and it has been widely used for decades, we first explored whether use of NPH itself might be associated with cancer risk. These analyses, using Poisson regression, were conducted among a cohort of users of NPH with no prescription for insulin in the 12 months prior to their first NPH prescription ($n = 46,390$). (Note that these analyses included new users at KPSC from 2001–2008 and at KPNC from 1996–2008 and thus included more than the 39,708 new users of NPH for the period 2001–2008 that were included in our main analyses.) We saw no evidence of an association with duration of NPH use and risk of colorectal, prostate, or all cancers combined. Compared with risk with <2 years of NPH use, there was some suggestion of a very modest increase in risk of breast cancer associated with ≥5 years of NPH use (Supplementary Table 4). The risk ratio was 1.2 (95% CI 0.9–1.6) when we calculated duration based on time between prescriptions and 1.6 (1.0–2.4) when we calculated duration by summing days supply for each prescription. Given the lack of a strong association between duration of NPH use and cancer risk and that we found little evidence for large differences in prior NPH use at the time of first eligible glargine versus first eligible NPH prescription, we used NPH with all durations combined as the primary comparison for our analyses of glargine use.

We found little evidence of confounding by BMI, race/ethnicity, income, diabetes

Table 1—*Selected characteristics at first eligible glargine or NPH prescription*[a]

	Full cohort: ever users of glargine or NPH				New users of insulin[b]			
	Glargine users (*n* = 27,418)		NPH users (*n* = 100,757)		Glargine users (*n* = 6,548)		NPH users (*n* = 39,708)	
	n	%	*n*	%	*n*	%	*n*	%
Calendar year								
2001	645	2.4	36,005	35.7	33	0.5	2,286	5.8
2002	1,834	6.7	10,316	10.2	170	2.6	4,319	10.9
2003	2,678	9.8	10,012	9.9	349	5.3	4,323	10.9
2004	2,382	8.7	8,126	8.1	360	5.5	4,409	11.1
2005	3,037	11.1	8,136	8.1	552	8.4	4,900	12.3
2006	4,342	15.8	8,025	8.0	1,057	16.1	5,211	13.1
2007	6,014	21.9	10,431	10.4	1,784	27.2	7,572	19.1
2008	6,486	23.7	9,706	9.6	2,243	34.3	6,688	16.8
Age (years)								
18–29	2,653	9.7	3,832	3.8	213	3.3	900	2.3
30–39	2,594	9.5	7,356	7.3	380	5.8	2,981	7.5
40–49	5,147	18.8	15,380	15.3	1,258	19.2	6,551	16.5
50–59	7,830	28.6	27,311	27.1	2,156	32.9	11,772	29.6
60–69	5,666	20.7	26,118	25.9	1,545	23.6	10,074	25.4
≥70	3,528	12.9	20,760	20.6	996	15.2	7,430	18.7
Sex								
Female	12,862	46.9	50,693	50.3	2,869	43.8	19,591	49.3
Male	14,555	53.1	50,063	49.7	3,679	56.2	20,117	50.7
Missing	1	0.0	1	0.0	0.0	0.00	0.0	0.0
Race/ethnicity								
Asian/Pacific	1,748	6.4	7,295	7.2	491	7.5	3,422	8.6
Black	2,840	10.4	13,090	13.0	694	10.6	4,535	11.4
Hispanic	6,089	22.2	25,544	25.4	1,864	28.5	10,997	27.7
White	12,203	44.5	42,634	42.3	2,369	36.2	15,962	40.2
Other	353	1.3	1,398	1.4	86	1.3	546	1.4
Unknown	4,185	15.3	10,796	10.7	1,044	15.9	4,246	10.7
BMI (kg/m^2)[c]								
<19	184	0.7	199	0.2	46	0.7	131	0.3
19–24	3,483	12.7	4,475	4.4	745	11.4	2,636	6.6
25–29	5,537	20.2	9,925	9.9	1,475	22.5	6,413	16.1
30–34	4,925	18.0	10,359	10.3	1,510	23.1	6,813	17.2
35–39	2,862	10.4	6,400	6.4	922	14.1	4,307	10.9
40–44	1,556	5.7	4,328	4.3	479	7.3	2,719	6.9
≥45	882	3.2	2,015	2.0	307	4.7	1,371	3.4
Unknown	7,989	29.1	63,056	62.6	1,064	16.2	15,318	38.6
BMI (kg/m^2)[d]								
<19	184	1.0	199	0.5	46	0.8	131	0.5
19–24	3,483	17.9	4,475	11.9	745	13.6	2,636	10.8
25–29	5,537	28.5	9,925	26.3	1,475	26.9	6,413	26.3
30–34	4,925	25.4	10,359	27.5	1,510	27.5	6,813	27.9
35–39	2,862	14.7	6,400	17.0	922	16.8	4,307	17.7
40–44	1,556	8.0	4,328	11.5	479	8.7	2,719	11.2
≥45	882	4.5	2,015	5.3	307	5.6	1,371	5.6
Income								
Low[e]	11,174	40.8	47,699	47.3	2,749	42.0	18,745	47.2
High	12,786	46.6	46,230	45.9	2,893	44.2	18,673	47.0
Missing	3,458	12.6	6,828	6.8	906	13.8	2,290	5.8
Smoking[f]								
Current user	4,018	14.7	13,886	13.8	864	13.2	6,155	15.5
Never user	15,223	55.5	45,768	45.4	3,778	57.7	20,245	51.0
Quit/former	5,425	19.8	19,233	19.1	1,471	22.5	8,171	20.6

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Table 1—*Continued*

	Full cohort: ever users of glargine or NPH				New users of insulin[b]			
	Glargine users (*n* = 27,418)		NPH users (*n* = 100,757)		Glargine users (*n* = 6,548)		NPH users (*n* = 39,708)	
	n	%	*n*	%	*n*	%	*n*	%
Passive	272	1.0	705	0.7	61	0.9	302	0.8
Not asked	32	0.1	84	0.1	9	0.1	34	0.1
Missing	2,448	8.9	21,081	20.9	365	5.6	4,801	12.0
Smoking[g]								
Current user	4,018	16.1	13,886	17.4	864	14.0	6,155	17.6
Never user	15,223	61.0	45,768	57.5	3,778	61.2	20,245	58.1
Quit/former	5,425	21.8	19,233	24.2	1,471	23.8	8,171	23.4
Passive	272	1.1	705	0.9	61	1.0	302	0.9
Creatinine (mg/dL)[h]								
Normal	20,529	74.9	74,857	74.3	5,035	76.9	30,016	75.6
Elevated	6,440	23.5	24,190	24.0	1,405	21.5	9,255	23.3
Missing	449	1.6	1,710	1.7	108	1.6	437	1.1
HbA_{1c} (%)[i]								
<7	3,964	14.5	15,843	15.7	550	8.4	3,871	9.8
7–7.9	5,947	21.7	20,910	20.8	967	14.8	5,851	14.7
8–8.9	5,908	21.5	19,749	19.6	1,342	20.5	7,628	19.2
9–9.9	4,212	15.4	14,938	14.8	1,067	16.3	6,870	17.3
≥10	6,974	25.4	27,480	27.3	2,444	37.3	14,723	37.1
Missing	413	1.5	1,837	1.8	178	2.7	765	1.9
Diagnosis of diabetes type[j]								
Type 1 only	1,878	6.9	2,789	2.8	108	1.6	280	0.7
Type 2 only	15,293	55.8	68,578	68.1	5,663	86.5	34,203	86.1
Both	9,909	36.1	25,248	25.1	646	9.9	4,358	11.0
Missing	338	1.2	4,142	4.0	131	2.0	867	2.2
Diabetes medication use[k]								
Metformin	9,645	35.2	40,670	40.4	3,865	59.0	22,936	57.8
Sulfonylureas	10,250	37.4	47,454	47.1	4,634	70.8	29,078	73.2
TZDs	4,905	17.9	15,789	15.7	2,019	30.8	9,307	23.4
Other diabetes drugs	556	2.0	1,822	1.8	231	3.5	1,059	2.7
Insulin								
NPH	10,680	39.0	44,036	43.7	0	0	0	0
Glargine	4,440	16.2	1,045	1.0	0	0	0	0
Short-acting	12,791	46.7	33,190	32.9	0	0	0	0
Long-acting, other	1,197	4.4	1,748	1.7	0	0	0	0

TZD, thiazolidinediones. [a]First eligible prescription was the first filled prescription that met all of the following requirements: dispensed in May 2001 or later, was the 2nd filled prescription for that medication within a 6-month period, and the recipient was ≥18 years of age and had 12 months of health plan membership and pharmacy benefits. [b]No prescription for any insulin in the 12 months prior to the first prescription for NPH or glargine. [c]BMI measures taken within 24 months before or after 1st eligible prescription. [d]Restricted to those with known BMI. [e]Low income is defined as median household income below the cohort average. [f]Based on earliest smoking data available. [g]Restricted to those with known smoking. [h]Elevated creatinine value (≥1.4 for women and ≥1.5 for men) closest to 1st eligible prescription. [i]Closest value prior to 1st eligible prescription. [j]Any diagnosis within 24 months prior to 1st eligible prescription. [k]In the 12 months prior to 1st eligible prescription.

type, HbA_{1c} levels, or ever use of other diabetes medications (Supplementary Tables 5 and 11). All analyses, therefore, were adjusted for KP region, age, sex (for colorectal cancer and all sites combined), year of cohort entry, use of metformin, and use of other insulins (short acting and other long acting). Metformin and other insulins were included because of interest by the European Medicines Agency in seeing models adjusted for these variables.

Among our full cohort of 115,514 glargine or NPH users, there was little support for an increased risk for prostate or colorectal cancer or all cancer sites combined associated with use of glargine (Tables 2–4, and Supplementary Table 12). However, there was a suggestion of a modestly increased risk of breast cancer among users of glargine for ≥2 years both among those who had and those who had not also used NPH (Table 2).

To examine whether switching to glargine after a history of using another long-acting insulin increased the risk of cancer, we looked at ever use of glargine and duration of glargine use among users of NPH at baseline (*n* = 99,506). We saw no evidence of an increase in risk for

Table 2—*HRs for breast cancer associated with ever use and with duration of glargine use among all users of NPH or glargine, among NPH users at baseline, and among new users of insulin at baseline*[a]

	Ever users of glargine or NPH				NPH insulin users at baseline				New insulin users at baseline			
Insulin[b]	Events	Person-years	HR[a]	95% CI	Events	Person-years	HR[a]	95% CI	Events	Person-years	HR[a]	95% CI
Ever use of glargine												
None (NPH only)	779	192,681.7	1.0	Ref.	779	192,681.7	1.0	Ref.	217	60,868.1	1.0	Ref.
Glargine[c]	131	37,365.6	1.0	0.9–1.3	56	17,074.0	0.9	0.7–1.2	52	10,614.8	1.3	1.0–1.8
Ever use of glargine												
None (NPH only)	779	192,681.7	1.0	Ref.	NA	NA	NA	NA	217	60,868.1	1.0	Ref.
Glargine only	68	17,293.9	1.2	1.0–1.6	NA	NA	NA	NA	33	6,402.4	1.3	0.9–2.0
Glargine and NPH	63	20,071.7	0.9	0.7–1.1	NA	NA	NA	NA	19	4,212.5	1.3	0.8–2.0
Duration of glargine[d]												
None (NPH only)	779	192,681.7	1.0	Ref.	779	192,681.7	1.0	Ref.	217	60,868.1	1.0	Ref.
<2 years glargine[c]	76	23,770.0	0.9	0.7–1.2	36	10,964.2	0.9	0.6–1.3	36	7,941.9	1.2	0.8–1.7
≥2 years glargine[c]	55	13,595.6	1.2	0.9–1.6	20	6,109.7	0.9	0.6–1.4	16	2,673.0	1.6	1.0–2.8
Duration of glargine[d]												
None (NPH only)	779	192,681.7	1.0	Ref.	NA	NA	NA	NA	217	60,868.1	1.0	Ref.
<2 years glargine only	35	11,095.1	1.0	0.7–1.4	NA	NA	NA	NA	22	4,777.6	1.2	0.7–1.9
≥2 years glargine only	33	6,198.9	1.6	1.1–2.4	NA	NA	NA	NA	11	1,624.8	1.7	0.9–3.2
Glargine and NPH	63	20,071.7	0.9	0.7–1.2	NA	NA	NA	NA	19	4,212.5	1.3	0.8–2.1

NA, not applicable among prevalent users of NPH at baseline. [a]HRs calculated using Cox regression; adjusted for site (KPNC, KPSC), calendar year of entry (2001, 2002, 2003, 2004, 2005, 2006, 2007, and 2008), age (18–34, 35–44, 45–54, 55–64, 65–74, and ≥75 years), metformin (ever vs. never), and insulin (ever vs. never long-acting, ever vs. never short-acting). [b]Insulin use treated as time varying. [c]Glargine users include those who used glargine alone as well as those who had also used NPH. [d]Duration calculated by adding the days between prescriptions; if the number of days between two prescriptions was >6 months, then the number of days counted for the earlier prescription was limited to 183.

breast, prostate, or colorectal cancer or all cancer sites combined associated with ever use of glargine, and there was little evidence that risk increased with longer duration of glargine use (Tables 2–4 and Supplementary Table 12).

To examine whether, among new users of insulin, initiating glargine use versus another long-acting insulin increased the risk of cancer, we compared risk in 6,548 new glargine users with risk among 39,708 new NPH users (Tables 2–4

Table 3—*HRs for prostate cancer associated with ever use and with duration of glargine use among all insulin users and among new users of insulin at baseline*[a]

	Ever users of glargine or NPH				NPH users at baseline				New insulin users at baseline			
Insulin[b]	Events	Person-years	HR[a]	95% CI	Events	Person-years	HR[a]	95% CI	Events	Person-years	HR[a]	95% CI
Ever use glargine												
None (NPH only)	675	179,445.3	1.0	Ref.	675	179,445.3	1.0	Ref.	226	59,132.9	1.0	Ref.
Glargine[c]	78	40,980.4	0.7	0.6–0.9	45	18,256.0	0.9	0.7–1.2	27	12,689.2	0.6	0.4–1.0
Ever use insulin												
None (NPH only)	675	179,445.3	1.0	Ref.	NA	NA	NA	NA	226	59,132.9	1.0	Ref.
Glargine only	31	19,937.7	0.6	0.4–0.9	NA	NA	NA	NA	13	8,012.3	0.5	0.3–0.9
Glargine and NPH	47	21,042.7	0.8	0.6–1.1	NA	NA	NA	NA	14	4,677.0	0.9	0.5–1.6
Duration of glargine[d]												
None (NPH only)	675	179,445.3	1.0	Ref.	675	179,445.3	1.0	Ref.	226	59,132.9	1.0	Ref.
<2 years glargine[c]	44	26,057.6	0.6	0.5–0.9	27	11,354.5	0.8	0.6–1.3	17	9,640.0	0.6	0.3–0.9
≥2 years glargine[c]	34	14,922.8	0.9	0.6–1.3	18	6,901.5	1.0	0.6–1.6	10	3,049.2	0.9	0.5–1.7
Duration of glargine[d]												
None (NPH only)	675	179,445.3	1.0	Ref.	NA	NA	NA	NA	226	59,132.9	1.0	Ref.
<2 years glargine only	16	13,037.6	0.5	0.3–0.8	NA	NA	NA	NA	7	6,135.2	0.4	0.2–0.0.8
≥2 years glargine only	15	6,900.1	0.9	0.5–1.5	NA	NA	NA	NA	6	1,877.1	0.8	0.4–1.9
Glargine and NPH	47	21,042.7	0.8	0.6–1.1	NA	NA	NA	NA	14	4,677.0	0.9	0.5–1.6

NA, not applicable among prevalent users of NPH at baseline. [a]HRs calculated using Cox regression; adjusted for site (KPNC, KPSC), calendar year of entry (2001, 2002, 2003, 2004, 2005, 2006, 2007, and 2008), age (18–34, 35–44, 45–54, 55–64, 65–74, and ≥75 years), metformin (ever vs. never), and insulin (ever vs. never long-acting, ever vs. never short-acting). [b]Insulin use treated as time varying. [c]Glargine users include those who used glargine alone as well as those who had also used NPH. [d]Duration calculated by adding the days between prescriptions; if the number of days between two prescriptions was >6 months, then the number of days counted for the earlier prescription was limited to 183.

Table 4—*HRs for colorectal cancer associated with ever use and with duration of glargine use among all insulin users and among new users of insulin at baseline*[a]

	Ever users of glargine or NPH				NPH users at baseline				New insulin users at baseline			
Insulin[b]	Events	Person-years	HR[a]	95% CI	Events	Person-years	HR[a]	95% CI	Events	Person-years	HR[a]	95% CI
Ever use glargine												
None (NPH only)	609	372,127.0	1.0	Ref.	609	372,127.0	1.0	Ref.	169	120,001.0	1.0	Ref.
Glargine[c]	91	78,346.0	1.0	0.8–1.2	32	35,330.0	0.7	0.5–1.0	36	23,304.1	1.1	0.8–1.6
Ever use insulin												
None (NPH only)	609	372,127.0	1.0	Ref.	NA	NA	NA	NA	169	120,001.0	1.0	Ref.
Glargine only	52	37,231.6	1.3	0.9–1.7	NA	NA	NA	NA	29	14,414.7	1.4	0.9–2.1
Glargine and NPH	39	41,114.4	0.8	0.5–1.1	NA	NA	NA	NA	7	8,889.4	0.7	0.3–1.4
Duration of glargine[d]												
None (NPH only)	609	372,127.0	1.0	Ref.	609	372,127.0	1.0	Ref.	169	120,001.0	1.0	Ref.
<2 years glargine[c]	55	49,827.6	0.9	0.7–1.2	18	22,318	0.6	0.4–1.0	31	17,581.9	1.3	0.9–1.9
≥2 years glargine[c]	36	28,518.4	1.1	0.8–1.5	14	13,011	0.9	0.5–1.5	5	5,722.2	0.7	0.3–1.6
Duration of glargine[d]												
None (NPH only)	609	372,127.0	1.0	Ref.	NA	NA	NA	NA	169	120,001.0	1.0	Ref.
<2 years glargine only	34	24,132.7	1.3	0.9–1.9	NA	NA	NA	NA	25	10,912.8	1.6	1.0–2.5
≥2 years glargine only	18	13,098.9	1.2	0.8–2.0	NA	NA	NA	NA	4	3,501.8	0.8	0.3–2.1
Glargine and NPH	39	41,114.4	0.8	0.5–1.1	NA	NA	NA	NA	7	8,889.4	0.7	0.3–1.4

NA, not applicable among prevalent users of NPH at baseline. [a]HRs calculated using Cox regression; adjusted for site (KPNC, KPSC), calendar year of entry (2001, 2002, 2003, 2004, 2005, 2006, 2007, and 2008), age (18–34, 35–44, 45–54, 55–64, 65–74, and ≥75 years), metformin (ever vs. never), and insulin (ever vs. never long-acting, ever vs. never short-acting). [b]Insulin use treated as time varying. [c]Glargine users include those who used glargine alone as well as those who had also used NPH. [d]Duration calculated by adding the days between prescriptions; if number of days between two prescriptions was >6 months, then the number of days counted for the earlier prescription was limited to 183.

and Supplementary Table 12). Compared with risk in NPH users (all durations combined), there was no increase in risk observed for prostate, colorectal, or all cancers combined associated with ever use of glargine. However, there was a suggestion of a modest increase in risk of breast cancer (hazard ratio [HR] 1.3 [95% CI 1.0–1.8]) (Tables 2–4 and Supplementary Table 12). There also was a suggestion that risk of breast cancer increased with increasing duration of glargine use. The HR for breast cancer was 1.2 (95% CI 0.8–1.7) for < 2 years of glargine use and 1.6 (95% CI 1.0–2.8) for ≥2 years of glargine use. Duration results were similar when looking at glargine use only among those who had not used NPH. There was little evidence for an increase in risk of prostate, colorectal, or all cancer sites combined associated with longer duration of glargine use.

Other subgroup and sensitivity analyses

In analyses restricted to individuals with 48 months of membership and pharmacy benefits prior to baseline, the HRs for breast, prostate, and colorectal cancer and all cancer sites combined were similar to those reported above (Supplementary Table 13).

In sensitivity analyses, we examined cancer risk associated with duration of glargine use when duration was calculated by summing days supply for each prescription. Results were generally similar to those in our main analyses with duration calculated as time between prescriptions, although among new insulin users the HR for breast cancer associated with ≥2 years' duration of glargine was slightly more elevated (HR 2.1 or 2.2, depending on whether patients had also used NPH) (Supplementary Table 14).

In additional sensitivity analyses among new insulin users, follow-up was censored as in the main analyses and additionally when a patient stopped using glargine or NPH or when they switched to another long-acting insulin. As in our main analyses, these sensitivity analyses were adjusted for Kaiser Permanente region, calendar year, sex, age, metformin use, and use of short-acting insulin, although use of metformin and short-acting insulin was fixed at baseline and not treated as time varying. We generated HRs for the period <2 years and for the period ≥2 years after insulin initiation (Supplementary Table 15). In these analyses, there was no evidence that ≥2 years of glargine use vs. ≥2 years of NPH increased the risk of prostate or colorectal cancer. There was a suggestion of a modest increase in risk of breast cancer associated with ≥2 years of glargine vs. ≥2 years of NPH (HR 1.6 [95% CI 0.9–3.1]). The HR for all cancers combined associated with ≥2 years of glargine use vs. ≥2 years of NPH was 1.2 (95% CI 0.9–1.7).

CONCLUSIONS—In this population-based cohort study, we found limited support for an association between use of glargine and increased risk of cancer. Results among prevalent users of NPH, another long-acting insulin with similar indications for use, suggested that risk of cancer was not increased among those switching to glargine. Among new users of insulin, ever use or longer duration of use of glargine versus use of NPH was not associated with increased risk of prostate or colorectal cancer. However, there was an ~1.5- to 2.0-fold increase in risk of breast cancer associated with ≥2 years of glargine use. Given the small number of breast cancer cases with ≥2 years of glargine use among the new users, these estimates were imprecise. In addition, these results conflict with the findings in the full cohort and among prevalent users of NPH. We believe it is implausible that duration of glargine use would be associated with risk of breast cancer among new users but not prevalent users of insulin and so believe that chance resulting from multiple comparisons is the most plausible explanation for the positive

association with breast cancer incidence among new glargine users.

Since the initial four European studies were published in June 2009 (1–4), several additional observational studies have reported results on the association between use of glargine and cancer risk (6–14). Among all studies, only a small number reported results for individual cancers. Breast cancer–specific results have been reported for seven study populations (2,4,6,9,10,12–14). In three studies (6,9,12), risk was weakly to modestly higher among glargine users or a subset of glargine users (e.g., users of glargine only or long-term users of insulin) than in users of other insulin, whereas in two studies (4,13) the risk was modestly lower and in one study (10) there was no difference in risk. The eighth was the Swedish study published in 2009 (2), which found an increased risk of breast cancer. However, in subsequent analyses with an expanded cohort and extended follow-up, the initial finding was attenuated or disappeared, depending on the time periods examined (7,14). Two studies (9,12) found an elevated risk of prostate cancer associated with glargine use, while one (10) found no association. Two studies reported a decrease in risk of colon or colorectal cancer (10,12).

An analysis combining results from 10,880 patients in 31 different clinical trials, mostly of very short duration of glargine use, found that glargine was not associated with an increased risk of breast, colon, or prostate cancer, although the number of cancer cases at these sites was small and risk estimates were imprecise (15). However, the strongest evidence to date bearing on the potential carcinogenicity of glargine comes from a recent analysis of the ORIGIN (Outcome Reduction With Initial Glargine Intervention) trial, which was conducted among patients with cardiovascular risk factors plus impaired fasting glucose, impaired glucose tolerance, or newly diagnosed type 2 diabetes and compared outcomes in 6,254 patients randomized to glargine with outcomes in 6,273 patients randomized to standard care (16). After a median of 6.2 years of follow-up, no increased risk of breast, prostate, or colon cancer was observed among patients in the glargine arm. For breast cancer specifically, there were exactly the same number of cases—28—diagnosed among those assigned to receive glargine and those assigned to receive standard care, although these results included both men and women.

The differences in results across studies may in part be explained by chance, different study designs or study populations, different comparison groups and adjustment for covariates, different practice patterns for diabetes management, or different periods of follow-up. Limitations of all studies include only recent and short-term use of glargine and a small number of cancers at specific sites. In addition, several observational studies had incomplete information on potentially important confounders.

Our study was subject to the above limitations as well. Glargine was available for use in the U.S. only as of May 2001, and ~60% of glargine users in our cohort initiated use in 2006 or later. We therefore were able only to examine the association between relatively recent and short-term use of glargine and cancer risk. The induction period for many carcinogens is often years to decades. Thus, this study of relatively recent and short-term use would miss effects that require longer exposure or follow-up to become evident. While the study was conducted in a large cohort of patients with diabetes, we had relatively few glargine-exposed cancer cases at the sites of interest, limiting our precision, especially for risk estimates associated with particular durations of use.

We lacked complete information on several potentially important confounders on the full cohort. However, in analyses restricted to individuals with information on race/ethnicity, type of diabetes, duration of diabetes, BMI, and smoking, we found little evidence of confounding by these factors.

Although guidelines at Kaiser Permanente for insulin initiation and management are generally similar to those recommended by the American Diabetes Association (16,17), practice patterns may differ from those in other medical care settings. For example, in a study of insulin users conducted in the U.S. Medicare population, ~40% used glargine and 60% used only a nonglargine insulin (10). However, practice patterns will only bias results if they are related to unmeasured risk factors for the cancers of interest.

There are several strengths of this cohort study. First, enrollees of KPNC and KPSC receive virtually all of their health care from the prepaid, integrated health plans. In addition, the memberships include >730,000 patients with diabetes. Computerized clinical records allow for the identification of patients with diabetes based on diagnoses, laboratory tests, and pharmacy data, and the plans have high-quality cancer registries. This study is also strengthened by the availability of electronic pharmacy records for data on medication use. By requiring patients to fill two prescriptions within a 6-month period, we increased the likelihood that those classified as users actually took the medications of interest.

In conclusion, our results do not support an association between relatively short-term use of glargine and increased risk of colorectal or prostate cancer or all cancer sites combined. These results are consistent with and complementary to the results of ORIGIN, the only randomized clinical trial with a large number of participants and follow-up extending more than a few years. Our finding of a modest increase in risk of breast cancer associated with ≥2 years of glargine among new insulin users should be viewed cautiously. Given study limitations, particularly the ability to examine only very recent and short-term glargine use, additional follow-up of this cohort and others will be needed to determine whether glargine is associated with an increase in breast or other forms of cancer.

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The opinions expressed are those of the authors.

L.A.H. designed the study, interpreted the results, and wrote, reviewed, and edited the manuscript. K.N.D. and C.P.Q. designed the study, interpreted results, and reviewed and edited the manuscript. A.C. collected, analyzed, and interpreted data and reviewed and edited the manuscript. S.K.V.D.E. and N.S.W. designed the study, interpreted results, and reviewed and edited the manuscript. A.F. designed the study, interpreted the results, and wrote, reviewed, and edited the manuscript. L.A.H. 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.

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References

1. Hemkens LG, Grouven U, Bender R, et al. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. Diabetologia 2009;52:1732–1744
2. Jonasson JM, Ljung R, Talbäck M, Haglund B, Gudbjörnsdòttir S, Steineck G. Insulin glargine use and short-term incidence of malignancies-a population-based follow-up study in Sweden. Diabetologia 2009;52:1745–1754
3. Colhoun HM; SDRN Epidemiology Group. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. Diabetologia 2009;52:1755–1765
4. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 2009;52:1766–1777
5. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer 2009;16:1103–1123
6. Suissa S, Azoulay L, Dell'Aniello S, Evans M, Vora J, Pollak M. Long-term effects of insulin glargine on the risk of breast cancer. Diabetologia 2011;54:2254–2262
7. Ljung R, Talbäck M, Haglund B, Jonasson JM, Gudbjörnsdòttir S, Steineck G. Insulin glargine use and short-term incidence of breast cancer - a four-year population-based observation. Acta Oncol 2012;51:400–402
8. Blin P, Lassalle R, Dureau-Pournin C, et al. Insulin glargine and risk of cancer: a cohort study in the French National Healthcare Insurance Database. Diabetologia 2012;55:644–653
9. Lind M, Fahlén M, Eliasson B, Odén A. The relationship between the exposure time of insulin glargine and risk of breast and prostate cancer: an observational study of the time-dependent effects of antidiabetic treatments in patients with diabetes. Prim Care Diabetes 2012;6:53–59
10. Morden NE, Liu SK, Smith J, Mackenzie TA, Skinner J, Korc M. Further exploration of the relationship between insulin glargine and incident cancer: a retrospective cohort study of older Medicare patients. Diabetes Care 2011;34:1965–1971
11. Mannucci E, Monami M, Balzi D, et al. Doses of insulin and its analogues and cancer occurrence in insulin-treated type 2 diabetic patients. Diabetes Care 2010;33:1997–2003
12. Ruiter R, Visser LE, van Herk-Sukel MP, et al. Risk of cancer in patients on insulin glargine and other insulin analogues in comparison with those on human insulin: results from a large population-based follow-up study. Diabetologia 2012;55:51–62
13. Chang CH, Toh S, Lin JW, et al. Cancer risk associated with insulin glargine among adult type 2 diabetes patients—a nationwide cohort study. PLoS ONE 2011;6:e21368
14. Ljung R, Talbäck M, Haglund B, Jonasson JM, Gudbjörnsdòttir S, Steineck G. Insulin glargine use and short-term incidence of malignancies - a three-year population-based observation. Acta Oncol 2011;50:685–693
15. Home PD, Lagarenne P. Combined randomised controlled trial experience of malignancies in studies using insulin glargine. Diabetologia 2009;52:2499–2506
16. Gerstein HC, Bosch J, Dagenais GR, et al.; ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367:319–328
17. Nathan DM, Buse JB, Davidson MB, et al.; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32:193–203