

SUPPLEMENTARY DATA

Supplementary Table 1. Time from first eligible prescription to end of follow-up (all users).

Insulin	Number of patients	Years of follow-up ¹			
		25 th percentile	50 th percentile	75 th percentile	Maximum
Glargine	27,418	1.36	2.32	3.91	8.56
NPH	100,757	1.71	3.56	6.54	8.63

¹From first eligible prescription to any cancer, termination of membership/pharmacy benefits, or end of study period (Dec 2009), whichever came first

Supplementary Table 2. Cumulative years¹ of use of glargine, NPH and other DM medications starting from first eligible glargine or NPH prescription to end of follow-up².

Medication	Glargine User (n= 27,418)					NPH User (n= 100,757)				
	%	25 th percentile	50 th percentile	75 th percentile	Maximum	%	25 th percentile	50 th percentile	75 th percentile	Maximum
Glargine	100	0.55	1.20	2.19	8.41	15	0.41	1.10	2.32	8.56
NPH	17	0.23	0.50	1.23	7.45	100	0.54	1.40	3.01	8.62
Other insulin										
Long-acting	2	0.09	0.27	0.66	6.27	1	0.16	0.30	0.82	7.94
Short-acting	75	0.49	1.13	2.22	8.52	74	0.44	1.26	2.90	8.62
Metformin	40	0.73	1.37	2.19	8.04	48	0.82	1.64	3.34	8.62
Sulfonylurea	34	0.68	1.31	2.19	8.51	47	0.82	1.64	3.18	8.62
TZDs	19	0.55	1.10	2.19	7.78	21	0.55	1.37	2.74	8.61

¹Calculated by summing the recorded days supply for each prescription

²Date of any cancer diagnosis, termination of membership/pharmacy benefits, or end of study period (Dec 2009), whichever came first

SUPPLEMENTARY DATA

Supplementary Table 3. Incidence rates¹ of invasive cancer, study cohort vs. SEER² California.

Cancer site	SEER California	KP Study Population	
	Incidence ¹	Incidence ¹	95% CI
Breast (female)	123.3	137.6	126.6 - 148.7
Prostate	146.3	97.5	90.5 - 104.5
Colorectal	44.2	53.9	49.5 - 58.4
Melanoma	23.2	17.8	13.2 - 22.3
Lung	58.4	47.2	43.4 - 51.0
Bladder ³	20.1	18.8	16.5 - 21.2
Non-Hodgkin Lymphoma	18.5	23.0	19.3 - 26.7
Kidney	13.4	18.9	16.2 - 21.7
Liver	7.4	21.5	18.7 - 24.3
Pancreas	11.3	25.6	22.6 - 28.6
All cancers	444.9	450.1	434.8 - 465.3

¹Per 100,000 person years, standardized to the age and sex distribution of the 2000 US Census

² National Cancer Institutes Surveillance, Epidemiology and End Results (SEER) program of registries.

These are incidence rates reported by SEER for the state of California.

³ Includes in situ cancers

SUPPLEMENTARY DATA

Supplementary Table 4. Rate ratios (RR) for duration of NPH use among new insulin users¹.

	Duration based on Time Between Prescriptions				Duration based on Day Supply			
	N	Person yrs	RR ²	95% CI	N	Person yrs	RR ²	95% CI
Breast								
<2 yrs	155	47,366.1	1.0	Reference	229	66,966.3	1.0	Reference
2-4 yrs	123	30,302.5	1.1	0.9-1.4	85	19,429.4	1.1	0.9-1.5
5+ yrs	61	12,650.1	1.2	0.9-1.6	25	3,922.9	1.6	1.0-2.4
Prostate								
<2 yrs	148	44,382.4	1.0	Reference	233	63,770.9	1.0	Reference
2-4 yrs	123	30,594.7	1.1	0.9-1.4	70	19,611.1	0.9	0.7-1.1
5+ yrs	54	12,426.8	1.0	0.7-1.4	22	4,022.0	1.2	0.8-1.9
Colorectal								
<2 yrs	116	91,748.5	1.0	Reference	171	130,737.1	1.0	Reference
2-4 yrs	90	60,897.2	1.0	0.8-1.3	68	39,040.5	1.2	0.9-1.5
5+ yrs	44	25,076.9	1.1	0.8-1.5	11	7,944.9	0.8	0.5-1.6
All Cancer								
<2 yrs	1,103	91,748.5	1.0	Reference	1,612	130,737.1	1.0	Reference
2-4 yrs	808	60,897.2	0.9	0.9-1.1	567	39,040.5	1.0	0.9-1.1
5+ yrs	396	25,076.9	0.9	0.9-1.2	128	7,944.9	1.0	0.9-1.3

¹NPH new user cohort n=46,390 (KPNC n=27,916 for 1996-2008, KPSC n=18,474 for 2001-2008)

²Calculated using Poisson regression; RRs adjusted for age and sex

SUPPLEMENTARY DATA

Supplementary Table 5. Analyses of potential confounding by BMI, restricted to those with BMI available (n=48,301).

		Models WITHOUT BMI			Models WITH BMI			Models WITHOUT BMI			Models WITH BMI		
		ALL Users			All Users			New Users			NEW Users		
		HR ¹	Lower	Upper	HR ¹	Lower	Upper	HR ¹	Lower	Upper	HR ¹	Lower	Upper
BREAST													
Ever Use Insulin	GLG only	1.26	0.89	1.79	1.30	0.92	1.85	1.43	0.92	2.21	1.44	0.93	2.23
	Both NPH and GLG	0.89	0.50	1.59	0.93	0.52	1.65	1.28	0.64	2.58	1.31	0.65	2.63
Duration based on	GLG <2 yrs	1.08	0.78	1.51	1.12	0.80	1.57	1.30	0.86	1.97	1.32	0.87	2.00
days supply	GLG ≥2 yrs	1.67	0.83	3.35	1.70	0.85	3.41	2.30	0.90	5.88	2.31	0.90	5.90
PROSTATE													
Ever Use Insulin	GLG only	0.43	0.25	0.74	0.43	0.25	0.74	0.35	0.16	0.77	0.35	0.16	0.77
	Both NPH and GLG	1.01	0.54	1.89	1.01	0.54	1.88	0.99	0.43	2.30	0.99	0.43	2.29
Duration based on	GLG <2 yrs	0.56	0.36	0.87	0.56	0.36	0.87	0.46	0.25	0.87	0.46	0.25	0.87
days supply	GLG ≥2 yrs	0.70	0.22	2.23	0.70	0.22	2.24	1.01	0.24	4.21	1.01	0.24	4.25
COLORECTAL													
Ever Use Insulin	GLG only	1.28	0.87	1.87	1.30	0.89	1.91	1.31	0.82	2.10	1.32	0.83	2.11
	Both NPH and GLG	0.78	0.39	1.54	0.79	0.40	1.57	0.64	0.23	1.77	0.66	0.24	1.81
Duration based on	GLG <2 yrs	1.11	0.77	1.59	1.13	0.78	1.63	1.21	0.77	1.88	1.22	0.78	1.90
days supply	GLG ≥2 yrs	1.30	0.56	3.01	1.30	0.56	3.03	0.46	0.06	3.34	0.45	0.06	3.32
ALL CANCER													
Ever Use Insulin	GLG only	1.09	0.94	1.25	1.08	0.94	1.25	1.03	0.85	1.24	1.03	0.85	1.24
	Both NPH and GLG	0.97	0.78	1.21	0.97	0.78	1.21	1.18	0.88	1.56	1.17	0.88	1.56
Duration based on	GLG <2 yrs	1.02	0.90	1.17	1.02	0.90	1.17	1.04	0.87	1.23	1.03	0.87	1.23
days supply	GLG ≥2 yrs	1.30	0.95	1.77	1.30	0.95	1.77	1.47	0.92	2.35	1.47	0.92	2.35

¹HRs for use of glargine (GLG): reference is use of NPH, all HRs adjusted for KP region, calendar year, age, sex (colorectal, all sites combined), metformin use (time-varying), other long-acting insulin (time-varying), short-acting insulin (time-varying).

SUPPLEMENTARY DATA

Supplementary Table 6. Analyses of potential confounding by race/ethnicity, restricted to those with race/ethnicity in electronic records (n=100,332).

		Models WITHOUT Race			Models WITH Race			Models WITHOUT Race			Models WITH Race		
		ALL Users			ALL Users			NEW Users			NEW Users		
		HR ¹	Lower	Upper	HR ¹	Lower	Upper	HR ¹	Lower	Upper	HR ¹	Lower	Upper
BREAST													
Ever Use Insulin	GLG only	1.30	0.99	1.70	1.27	0.97	1.66	1.41	0.96	2.08	1.40	0.95	2.07
	Both NPH and GLG	0.88	0.67	1.15	0.86	0.66	1.12	1.19	0.72	1.97	1.17	0.71	1.94
Duration based on days supply	GLG <2 yrs	1.00	0.80	1.24	0.98	0.79	1.21	1.20	0.84	1.70	1.19	0.84	1.69
	GLG ≥2 yrs	1.30	0.89	1.91	1.26	0.86	1.85	2.22	1.15	4.27	2.18	1.13	4.19
PROSTATE													
Ever Use Insulin	GLG only	0.63	0.43	0.93	0.64	0.44	0.94	0.51	0.28	0.92	0.50	0.28	0.91
	Both NPH and GLG	0.80	0.59	1.09	0.82	0.60	1.12	0.96	0.55	1.67	0.97	0.56	1.70
Duration based on days supply	GLG <2 yrs	0.61	0.45	0.81	0.62	0.46	0.83	0.67	0.43	1.05	0.67	0.43	1.05
	GLG ≥2 yrs	1.26	0.83	1.92	1.30	0.86	1.99	0.74	0.27	2.01	0.76	0.28	2.07
COLORECTAL													
Ever Use Insulin	GLG only	1.29	0.94	1.77	1.27	0.93	1.75	1.36	0.88	2.11	1.36	0.88	2.12
	Both NPH and GLG	0.70	0.49	0.99	0.69	0.48	0.98	0.61	0.27	1.38	0.60	0.26	1.37
Duration based on days supply	GLG <2 yrs	0.85	0.65	1.12	0.84	0.64	1.11	1.15	0.77	1.73	1.15	0.77	1.72
	GLG ≥2 yrs	1.36	0.87	2.12	1.33	0.85	2.09	0.62	0.15	2.53	0.62	0.15	2.54
ALL CANCER													
Ever Use Insulin	GLG only	1.06	0.95	1.18	1.03	0.92	1.16	1.03	0.87	1.22	1.03	0.87	1.21
	Both NPH and GLG	0.89	0.80	0.99	0.87	0.78	0.97	1.02	0.83	1.26	1.01	0.82	1.24
Duration based on days supply	GLG <2 yrs	0.92	0.84	1.00	0.90	0.82	0.98	1.00	0.86	1.15	0.99	0.86	1.14
	GLG ≥2 yrs	1.19	1.02	1.40	1.15	0.98	1.35	1.25	0.91	1.72	1.23	0.89	1.69

¹HRs for use of glargine (GLG): reference is use of NPH, all HRs adjusted for KP region, calendar year, age, sex (colorectal, all sites combined), metformin use (time-varying), other long-acting insulin (time-varying), short-acting insulin (time-varying).

SUPPLEMENTARY DATA

Supplementary Table 7. Analyses of potential confounding by income, restricted to those with income available in records (n=106,056).

		Models WITHOUT Income			Models WITH Income			Models WITHOUT Income			Models WITH Income		
		ALL Users			ALL Users			NEW Users			NEW Users		
			95% CI			95% CI			95% CI			95% CI	
		HR ¹	Lower	Upper	HR ¹	Lower	Upper	HR ¹	Lower	Upper	HR ¹	Lower	Upper
BREAST													
Ever Use Insulin	GLG only	1.25	0.95	1.65	1.25	0.95	1.64	1.42	0.97	2.09	1.42	0.96	2.09
	Both NPH and GLG	0.85	0.65	1.11	0.84	0.64	1.11	1.11	0.66	1.86	1.10	0.66	1.86
Duration based on days supply	GLG <2 yrs	0.96	0.77	1.20	0.96	0.77	1.19	1.15	0.80	1.64	1.15	0.80	1.64
	GLG ≥2 yrs	1.24	0.84	1.83	1.23	0.83	1.81	2.29	1.22	4.29	2.29	1.22	4.29
PROSTATE													
Ever Use Insulin	GLG only	0.48	0.31	0.74	0.48	0.31	0.74	0.44	0.24	0.82	0.44	0.24	0.82
	Both NPH and GLG	0.75	0.54	1.03	0.75	0.54	1.03	0.85	0.48	1.51	0.85	0.48	1.51
Duration based on days supply	GLG <2 yrs	0.51	0.37	0.70	0.51	0.37	0.70	0.56	0.35	0.90	0.56	0.35	0.90
	GLG ≥2 yrs	1.15	0.75	1.77	1.15	0.75	1.77	0.82	0.33	2.01	0.82	0.33	2.01
COLORECTAL													
Ever Use Insulin	GLG only	1.22	0.88	1.69	1.22	0.88	1.69	1.29	0.83	1.99	1.29	0.83	1.99
	Both NPH and GLG	0.78	0.56	1.09	0.78	0.56	1.09	0.60	0.26	1.36	0.60	0.26	1.36
Duration based on days supply	GLG <2 yrs	0.91	0.70	1.19	0.91	0.70	1.19	1.12	0.74	1.67	1.12	0.74	1.67
	GLG ≥2 yrs	1.20	0.75	1.91	1.19	0.75	1.91	0.55	0.13	2.25	0.55	0.13	2.25
ALL CANCER													
Ever Use Insulin	GLG only	0.99	0.88	1.11	0.99	0.88	1.11	0.98	0.82	1.15	0.98	0.82	1.15
	Both NPH and GLG	0.90	0.81	1.00	0.90	0.81	1.00	0.99	0.81	1.22	0.99	0.81	1.22
Duration based on days supply	GLG <2 yrs	0.89	0.82	0.98	0.89	0.82	0.98	0.95	0.82	1.10	0.95	0.82	1.10
	GLG ≥2 yrs	1.14	0.97	1.34	1.14	0.97	1.34	1.21	0.89	1.66	1.21	0.89	1.66

¹HRs for use of glargine (GLG): reference is use of NPH, all HRs adjusted for KP region, calendar year, age, sex (colorectal, all sites combined), metformin use (time-varying), other long-acting insulin (time-varying), short-acting insulin (time-varying).

SUPPLEMENTARY DATA

Supplementary Table 8. Analyses of potential confounding by DM type, restricted to those with DM type available in electronic records (n=111,113).

		Models WITHOUT DM Type			Models WITH DM Type			Models WITHOUT DM Type			Models WITH DM Type		
		ALL Users			All Users			New Users			NEW Users		
			95% CI			95% CI			95% CI			95% CI	
		HR ¹	Lower	Upper	HR ¹	Lower	Upper	HR ¹	Lower	Upper	HR ¹	Lower	Upper
BREAST													
Ever Use Insulin	GLG only	1.25	0.96	1.63	1.26	0.96	1.64	1.38	0.94	2.02	1.38	0.94	2.02
	Both NPH and GLG	0.86	0.66	1.13	0.86	0.66	1.13	1.23	0.75	2.01	1.23	0.75	2.01
Duration based on days supply	GLG <2 yrs	0.99	0.79	1.22	0.99	0.80	1.23	1.18	0.84	1.67	1.18	0.84	1.67
	GLG ≥2 yrs	1.21	0.82	1.78	1.22	0.83	1.80	2.26	1.21	4.24	2.25	1.20	4.21
PROSTATE													
Ever Use Insulin	GLG only	0.59	0.40	0.86	0.60	0.41	0.88	0.49	0.28	0.87	0.49	0.27	0.86
	Both NPH and GLG	0.78	0.57	1.07	0.80	0.58	1.08	0.91	0.53	1.59	0.91	0.52	1.58
Duration based on days supply	GLG <2 yrs	0.57	0.43	0.77	0.58	0.43	0.78	0.62	0.40	0.97	0.61	0.39	0.96
	GLG ≥2 yrs	1.23	0.81	1.85	1.26	0.84	1.91	0.83	0.34	2.03	0.82	0.33	2.01
COLORECTAL													
Ever Use Insulin	GLG only	1.28	0.94	1.74	1.26	0.93	1.72	1.41	0.93	2.13	1.42	0.94	2.15
	Both NPH and GLG	0.75	0.53	1.05	0.74	0.53	1.04	0.59	0.26	1.34	0.59	0.26	1.34
Duration based on days supply	GLG <2 yrs	0.94	0.72	1.21	0.93	0.72	1.20	1.21	0.82	1.78	1.21	0.82	1.78
	GLG ≥2 yrs	1.15	0.72	1.84	1.14	0.71	1.81	0.56	0.14	2.28	0.56	0.14	2.29
ALL CANCER													
Ever Use Insulin	GLG only	1.02	0.91	1.14	1.03	0.92	1.15	1.01	0.86	1.19	1.01	0.86	1.19
	Both NPH and GLG	0.89	0.80	1.00	0.90	0.81	1.00	1.02	0.83	1.25	1.02	0.83	1.25
Duration based on days supply	GLG <2 yrs	0.91	0.83	0.99	0.91	0.83	1.00	0.98	0.85	1.13	0.98	0.86	1.13
	GLG ≥2 yrs	1.15	0.99	1.35	1.16	0.99	1.36	1.24	0.91	1.69	1.24	0.91	1.69

¹HRs for use of glargine (GLG): reference is use of NPH, all HRs adjusted for KP region, calendar year, age, sex (colorectal, all sites combined), metformin use (time-varying), other long-acting insulin (time-varying), short-acting insulin (time-varying).

SUPPLEMENTARY DATA

Supplementary Table 9. Analyses of potential confounding by HbA1c, restricted to those with HbA1c levels available (n=113,301).

		Models WITHOUT HbA1c			Models WITH HbA1c			Models WITHOUT HbA1c			Models WITH HbA1c		
		ALL Users			ALL Users			NEW Users			NEW Users		
		HR ¹	Lower	Upper	HR ¹	Lower	Upper	HR ¹	Lower	Upper	HR ¹	Lower	Upper
BREAST													
Ever Use Insulin	GLG only	1.24	0.95	1.62	1.24	0.95	1.62	1.37	0.94	2.01	1.37	0.94	2.01
	Both NPH and GLG	0.87	0.66	1.13	0.87	0.67	1.14	1.29	0.80	2.08	1.29	0.80	2.08
Duration based on days supply	GLG <2 yrs	0.98	0.79	1.21	0.98	0.79	1.22	1.21	0.86	1.70	1.21	0.86	1.70
	GLG ≥2 yrs	1.23	0.84	1.81	1.24	0.84	1.81	2.25	1.20	4.21	2.25	1.20	4.21
PROSTATE													
Ever Use Insulin	GLG only	0.57	0.39	0.83	0.57	0.39	0.83	0.49	0.28	0.87	0.50	0.28	0.88
	Both NPH and GLG	0.78	0.58	1.06	0.78	0.58	1.06	0.90	0.52	1.56	0.90	0.52	1.56
Duration based on days supply	GLG <2 yrs	0.56	0.42	0.75	0.56	0.42	0.75	0.62	0.39	0.96	0.62	0.40	0.96
	GLG ≥2 yrs	1.22	0.82	1.83	1.23	0.82	1.85	0.82	0.34	2.03	0.83	0.34	2.04
COLORECTAL													
Ever Use Insulin	GLG only	1.30	0.96	1.77	1.30	0.96	1.77	1.41	0.93	2.13	1.41	0.93	2.13
	Both NPH and GLG	0.75	0.53	1.04	0.74	0.53	1.04	0.59	0.26	1.34	0.59	0.26	1.34
Duration based on days supply	GLG <2 yrs	0.92	0.71	1.19	0.92	0.71	1.19	1.21	0.82	1.77	1.21	0.82	1.77
	GLG ≥2 yrs	1.25	0.80	1.95	1.25	0.80	1.95	0.56	0.14	2.27	0.56	0.14	2.27
ALL CANCER													
Ever Use Insulin	GLG only	1.02	0.91	1.14	1.02	0.91	1.14	1.02	0.87	1.20	1.02	0.87	1.20
	Both NPH and GLG	0.90	0.81	1.00	0.90	0.81	1.00	1.06	0.86	1.29	1.06	0.87	1.29
Duration based on days supply	GLG <2 yrs	0.90	0.83	0.99	0.91	0.83	0.99	1.00	0.87	1.15	1.00	0.87	1.15
	GLG ≥2 yrs	1.16	1.00	1.36	1.17	1.00	1.36	1.28	0.94	1.73	1.28	0.94	1.73

¹HRs for use of glargine (GLG): reference is use of NPH, all HRs adjusted for KP region, calendar year, age, sex (colorectal, all sites combined), metformin use (time-varying), other long-acting insulin (time-varying), short-acting insulin (time-varying).

SUPPLEMENTARY DATA

Supplementary Table 10. Analyses of potential confounding by creatinine, restricted to those with creatinine available in records (n=113,416).

		Models WITHOUT Creatinine			Models WITH Creatinine			Models WITHOUT Creatinine			Models WITH Creatinine		
		ALL Users			ALL Users			NEW Users			NEW Users		
		95% CI			95% CI			95% CI			95% CI		
		HR ¹	Lower	Upper	HR ¹	Lower	Upper	HR ¹	Lower	Upper	HR ¹	Lower	Upper
BREAST													
Ever Use Insulin	GLG only	1.24	0.95	1.61	1.24	0.95	1.61	1.35	0.92	1.98	1.35	0.92	1.98
	Both NPH and GLG	0.87	0.67	1.14	0.87	0.67	1.13	1.28	0.79	2.07	1.28	0.79	2.07
Duration based on days supply	GLG <2 yrs	0.98	0.79	1.21	0.98	0.79	1.21	1.19	0.85	1.68	1.19	0.84	1.68
	GLG ≥2 yrs	1.24	0.85	1.82	1.24	0.85	1.82	2.26	1.21	4.23	2.25	1.20	4.22
PROSTATE													
Ever Use Insulin	GLG only	0.57	0.39	0.83	0.57	0.39	0.84	0.49	0.28	0.87	0.50	0.28	0.88
	Both NPH and GLG	0.77	0.57	1.05	0.77	0.57	1.05	0.90	0.52	1.57	0.90	0.52	1.57
Duration based on days supply	GLG <2 yrs	0.55	0.41	0.74	0.55	0.41	0.74	0.62	0.39	0.96	0.62	0.40	0.97
	GLG ≥2 yrs	1.24	0.83	1.86	1.25	0.84	1.88	0.83	0.34	2.04	0.84	0.34	2.05
COLORECTAL													
Ever Use Insulin	GLG only	1.30	0.95	1.76	1.30	0.96	1.77	1.40	0.93	2.11	1.41	0.93	2.13
	Both NPH and GLG	0.74	0.53	1.04	0.75	0.53	1.04	0.58	0.25	1.32	0.58	0.26	1.33
Duration based on days supply	GLG <2 yrs	0.92	0.71	1.19	0.92	0.71	1.19	1.20	0.81	1.76	1.20	0.82	1.77
	GLG ≥2 yrs	1.24	0.80	1.94	1.25	0.80	1.95	0.55	0.13	2.24	0.55	0.14	2.26
ALL CANCER													
Ever Use Insulin	GLG only	1.02	0.91	1.14	1.02	0.91	1.14	1.01	0.86	1.19	1.01	0.86	1.19
	Both NPH and GLG	0.88	0.80	0.98	0.89	0.80	0.98	1.04	0.85	1.27	1.04	0.86	1.28
Duration based on days supply	GLG <2 yrs	0.90	0.82	0.98	0.90	0.82	0.98	0.99	0.86	1.14	0.99	0.86	1.14
	GLG ≥2 yrs	1.16	1.00	1.36	1.17	1.00	1.36	1.26	0.93	1.71	1.26	0.93	1.71

¹HRs for use of glargine (GLG): reference is use of NPH, all HRs adjusted for KP region, calendar year, age, sex (colorectal, all sites combined), metformin use time-varying), other long-acting insulin (time-varying), short-acting insulin (time-varying).

SUPPLEMENTARY DATA

Supplementary Table 11. Analyses of potential confounding by other DM medications (n=115,512).

		Models WITHOUT Other DM medications			Models WITH Other DM medications			Models WITHOUT Other DM medications			Models WITH Other DM medications		
		ALL Users			ALL Users			NEW Users			NEW Users		
		95% CI			95% CI			95% CI			95% CI		
		HR ¹	Lower	Upper	HR ¹	Lower	Upper	HR ¹	Lower	Upper	HR ¹	Lower	Upper
BREAST													
Ever Use Insulin	GLG only	1.22	0.94	1.60	1.21	0.93	1.58	1.35	0.92	1.97	1.38	0.94	2.03
	Both NPH and GLG	0.87	0.67	1.14	0.87	0.67	1.13	1.28	0.79	2.07	1.31	0.81	2.12
Duration based on days supply	GLG <2 yrs	0.97	0.78	1.20	0.96	0.78	1.19	1.19	0.84	1.68	1.22	0.86	1.72
	GLG ≥2 yrs	1.26	0.86	1.83	1.24	0.85	1.81	2.24	1.20	4.19	2.33	1.24	4.36
PROSTATE													
Ever Use Insulin	GLG only	0.58	0.40	0.84	0.57	0.39	0.83	0.48	0.27	0.86	0.48	0.27	0.85
	Both NPH and GLG	0.78	0.57	1.05	0.77	0.57	1.05	0.89	0.51	1.54	0.88	0.51	1.53
Duration based on days supply	GLG <2 yrs	0.56	0.42	0.75	0.56	0.42	0.75	0.61	0.39	0.95	0.60	0.39	0.95
	GLG ≥2 yrs	1.21	0.81	1.82	1.20	0.80	1.80	0.80	0.32	1.96	0.78	0.32	1.93
COLORECTAL													
Ever Use Insulin	GLG only	1.27	0.94	1.72	1.25	0.92	1.70	1.37	0.91	2.07	1.37	0.91	2.07
	Both NPH and GLG	0.76	0.55	1.06	0.76	0.54	1.06	0.67	0.31	1.44	0.68	0.32	1.47
Duration based on days supply	GLG <2 yrs	0.92	0.71	1.19	0.92	0.71	1.19	1.21	0.83	1.77	1.22	0.83	1.79
	GLG ≥2 yrs	1.23	0.78	1.91	1.21	0.78	1.90	0.53	0.13	2.18	0.54	0.13	2.20
ALL CANCER													
Ever Use Insulin	GLG only	1.01	0.90	1.13	1.02	0.91	1.14	1.00	0.85	1.17	1.01	0.86	1.19
	Both NPH and GLG	0.90	0.81	1.00	0.90	0.81	1.00	1.05	0.86	1.28	1.06	0.87	1.30
Duration based on days supply	GLG <2 yrs	0.90	0.83	0.99	0.91	0.83	0.99	0.99	0.86	1.13	1.00	0.87	1.15
	GLG ≥2 yrs	1.15	0.99	1.34	1.16	0.99	1.35	1.23	0.91	1.68	1.27	0.93	1.72

¹HRs for use of glargine (GLG): reference is use of NPH, all HRs adjusted for KP region, calendar year, age, sex (colorectal, all sites combined), metformin use time-varying), other long-acting insulin (time-varying), short-acting insulin (time-varying).

SUPPLEMENTARY DATA

Supplementary Table 12. Hazard ratios (HRs) for all cancer associated with ever use and with duration of glargine use among all insulin users and among new users of insulin at baseline¹.

Insulin	Ever Users of Glargine or NPH				NPH Users at Baseline				New Insulin Users at Baseline			
	Events	Pr-years	HR ¹	95% CI	Events	Pr-years	HR ¹	95% CI	Events	Pr-years	HR ¹	95% CI
Ever use glargine												
None (NPH only)	5,067	372,127.0	1.0	Ref	5,067	372,127.0	1.0	Ref	1,570	120,001.0	1.0	Ref
Glargine ³	784	78,346.0	0.9	0.9-1.0	351	35,330.0	0.9	0.8-1.0	286	23,304.1	1.0	0.9-1.2
Ever use insulin												
None (NPH only)	5,067	372,127.0	1.0	Ref	NA	NA	NA	NA	1,570	120,001.0	1.0	Ref
Glargine only	385	37,231.6	1.0	0.9-1.1	NA	NA	NA	NA	177	14,414.7	1.0	0.9-1.2
Glargine and NPH	399	41,114.4	0.9	0.8-1.0	NA	NA	NA	NA	109	8,889.4	1.0	0.9-1.3
Duration of glargine ⁴												
None (NPH only)	5,067	372,127.0	1.0	Ref	5,067	372,127.0	1.0	Ref	1,570	120,001.0	1.0	Ref
<2 yrs glargine ³	485	49,827.6	0.9	0.8-1.0	215	22,318.7	0.9	0.8-1.0	210	17,581.9	1.0	0.9-1.1
2+ yrs glargine ³	299	28518.4	1.0	0.9-1.1	136	13,011.2	1.0	0.8-1.2	76	5,722.2	1.1	0.9-1.4
Duration of glargine ⁴												
None (NPH only)	5,067	372,127.0	1.0	ref	NA	NA	NA	NA	1,570	120,001.0	1.0	Ref
<2 yrs glargine only	242	24,132.7	1.0	0.8-1.1	NA	NA	NA	NA	130	10,912.8	1.0	0.8-1.2
2+ yrs glargine only	143	13,098.9	1.1	0.9-1.3	NA	NA	NA	NA	47	3,501.8	1.1	0.8-1.5
Glargine and NPH	399	41,114.4	0.9	0.8-1.0	NA	NA	NA	NA	109	8889.4	1.0	0.9-1.3

¹HRs calculated using Cox regression; adjusted for site (KPNC, KPSC), calendar year of entry (2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008), age (18-34, 35-44, 45-54, 55-64, 65-74, 75+), metformin (ever vs. never), Insulin (ever vs. never long, ever vs. never short)

²Insulin use treated as time-varying.

³Glargine users include those who used glargine alone as well as those who had also used NPH

⁴Duration calculated by adding the days between prescriptions; if days between two prescriptions was > 6 months then the days counted for the earlier prescription was limited to 183.

NA = not applicable among prevalent users of NPH at baseline

SUPPLEMENTARY DATA

Supplementary Table 13. Hazard ratios (HRs) among patients with at least 48 months of membership and pharmacy benefits prior to cohort entry

		Events	ALL Users				Events	Pr-years	NEW Users					
			Pr-years	HR ¹	95% CI				Pr-years	HR ¹	95% CI			
					Lower	Upper					Lower	Upper		
BREAST														
Ever Use Insulin	NPH only	582	135854.6	1.0	Ref		162	41174.8	1.0	Ref				
	GLG only	36	8780.0	1.1	0.7	1.5	20	4504.5	1.0	0.6	1.7			
	Both NPH and GLG	55	15009.3	1.0	0.7	1.3	14	2791.6	1.3	0.8	2.3			
Duration based on days supply	GLG <2 yrs	70	19352.7	1.0	0.7	1.2	27	6282.0	1.0	0.7	1.6			
	GLG ≥2 yrs	21	4436.7	1.3	0.8	2.0	7	1014.1	1.8	0.8	3.9			
INVASIVE BREAST														
Ever Use Insulin	NPH only	484	135854.6	1.0	Ref		137	41174.8	1.0	Ref				
	GLG only	30	8780.0	1.1	0.8	1.7	16	4504.5	1.0	0.6	1.7			
	Both NPH and GLG	49	15009.3	1.1	0.8	1.4	13	2791.6	1.5	0.8	2.7			
Duration based on days supply	GLG <2 yrs	61	19352.7	1.0	0.8	1.4	23	6282.0	1.1	0.7	1.7			
	GLG ≥2 yrs	18	4436.7	1.3	0.8	2.1	6	1014.1	1.9	0.8	4.5			
PROSTATE														
Ever Use Insulin	NPH only	542	127647.6	1.0	Ref		180	42262.6	1.0	Ref				
	GLG only	14	10253.9	0.4	0.2	0.7	7	5694.3	0.3	0.1	0.7			
	Both NPH and GLG	36	15445.3	0.8	0.5	1.1	9	3174.6	0.8	0.4	1.5			
Duration based on days supply	GLG <2 yrs	31	20640.6	0.5	0.3	0.7	11	7720.4	0.4	0.2	0.7			
	GLG ≥2 yrs	19	5058.6	1.2	0.8	2.0	5	1148.6	1.0	0.4	2.5			
COLORECTAL														
Ever Use Insulin	NPH only	471	263502.2	1.0	Ref		128	83437.4	1.0	Ref				
	GLG only	28	19033.8	1.1	0.7	1.6	21	10198.9	1.2	0.8	2.0			
	Both NPH and GLG	28	30454.7	0.7	0.5	1.0	4	5966.2	0.5	0.2	1.4			
Duration based on days supply	GLG <2 yrs	41	39993.2	0.7	0.5	1.0	23	14002.4	1.0	0.7	1.6			
	GLG ≥2 yrs	15	9495.2	1.2	0.7	2.0	2	2162.7	0.7	0.2	2.8			
ALL CANCER														
Ever Use Insulin	NPH only	3,838	263502.2	1.0	Ref		1,167	83437.4	1.0	Ref				
	GLG only	210	19033.8	0.9	0.8	1.0	132	10198.9	1.0	0.8	1.2			
	Both NPH and GLG	309	30454.7	0.9	0.8	1.0	80	5966.2	1.1	0.9	1.4			
Duration based on days supply	GLG <2 yrs	394	39993.2	0.8	0.7	0.9	176	14002.4	1.0	0.8	1.1			
	GLG ≥2 yrs	125	9495.2	1.2	1.0	1.4	36	2162.7	1.3	0.9	1.9			

¹HRs for use of glargine (GLG): reference is use of NPH, all HRs adjusted for KP region, calendar year, age, sex (colorectal, all sites combined), metformin (ever vs. never), Insulin other long-acting insulin (time-varying), short-acting insulin (time-varying).

SUPPLEMENTARY DATA

Supplementary Table 14. Hazard ratios (HRs associated duration of glargine use based on days supply among all users of NPH or glargine, among NPH users at baseline, and among new users of insulin at baseline¹.

Insulin ²	Ever Users of Glargine or NPH				NPH Insulin Users at Baseline				New Insulin Users at Baseline			
	Events	Pr-years	HR ¹	95% CI	Events	Pr-years	HR ¹	95% CI	Events	Pr-years	HR ¹	95% CI
Breast												
Duration of glargine ⁴												
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 yrs glargine ³	101	30,638.1	1.0	0.8-1.2	43	13,881.4	0.9	0.6-1.2	41	9,233.2	1.2	0.8-1.7
2+ yrs glargine ³	30	6,727.5	1.3	0.9-1.8	13	3,192.6	1.1	0.6-1.9	11	1,381.7	2.2	1.2-4.2
Duration of glargine ⁴												
None (NPH only)	779	192,681.7	1.0	Ref	NA	NA	NA	NA	217	60,868.1	1.0	ref
<2 yrs glargine only	52	14,398.2	1.2	0.9-1.6	NA	NA	NA	NA	26	5,559.8	1.2	0.8-1.8
2+ yrs glargine only	16	2,895.7	1.6	1.0-2.7	NA	NA	NA	NA	7	842.6	2.1	1.0-4.6
Glargine and NPH	63	20,071.7	0.9	0.7-1.2	NA	NA	NA	NA	19	4212.5	1.3	0.8-2.1
Prostate												
Duration of glargine ⁴												
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 yrs glargine ³	52	33,093.4	0.6	0.4-0.8	31	14,352.2	0.8	0.5-1.1	22	11,096.8	0.6	0.4-1.0
2+ yrs glargine ³	26	7,887.0	1.3	0.9-1.9	14	3,903.8	1.4	0.8-2.4	5	1,592.5	0.8	0.3-2.0
Duration of glargine ⁴												
None (NPH only)	675	179,445.3	1.0	Ref	NA	NA	NA	NA	226	59,132.9	1.0	Ref
<2 yrs glargine only	20	16,542.1	0.5	0.3-0.7	NA	NA	NA	NA	11	7,083.1	0.5	0.3-0.9
2+ yrs glargine only	11	3,395.6	1.3	0.7-2.4	NA	NA	NA	NA	2	929.2	0.6	0.1-2.3
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
Colorectal												
Duration of glargine ⁴												
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 yrs glargine ³	70	63,731.5	0.9	0.7-1.2	24	28,233.6	0.7	0.4-1.0	34	20,329.9	1.2	0.8-1.8
2+ yrs glargine ³	21	14,614.5	1.2	0.8-1.9	8	7,096.3	0.9	0.4-1.8	2	2,974.2	0.5	0.1-2.2
Duration of glargine ⁴												
None (NPH only)	609	372,127.0	1.0	Ref	NA	NA	NA	NA	169	120,001.0	1.0	Ref
<2 yrs glargine only	42	30,940.3	1.2	0.9-1.7	NA	NA	NA	NA	27	12,642.9	1.5	0.9-2.3
2+ yrs glargine only	10	6,291.3	1.4	0.7-2.6	NA	NA	NA	NA	2	1,771.8	0.8	0.2-3.2
Glargine and NPH	39	41,114.4	0.8	0.5-1.1	NA	NA	NA	NA	7	8889.4	0.7	0.3-1.4
All Cancers												
Duration of glargine ⁴												
None (NPH only)	5,067	372,127.0	1.0	Ref	5,067	372,127.0	1.0	Ref	1,570	120,001.0	1.0	Ref
<2 yrs glargine ³	609	63,731.5	0.9	0.8-1.0	265	28,233.6	0.9	0.8-1.0	242	20,329.9	1.0	0.9-1.1
2+ yrs glargine ³	175	14,614.5	1.2	1.0-1.3	86	7,096.3	1.1	0.9-1.4	44	2,974.2	1.2	0.9-1.7

SUPPLEMENTARY DATA

Duration of glargine ⁴												
None (NPH only)	5,067	372,127.0	1.0	Ref	NA	NA	NA	NA	1,570	120,001.0	1.0	Ref
<2 yrs glargine only	304	30,940.3	1.0	0.8-1.1	NA	NA	NA	NA	151	12,642.9	1.0	0.8-1.2
2+ yrs glargine only	81	6,291.3	1.3	1.0-1.6	NA	NA	NA	NA	26	1,771.8	1.2	0.8-1.8
Glargine and NPH	399	41,114.4	0.9	0.8-1.0	NA	NA	NA	NA	109	8889.4	1.0	0.9-1.3

¹HRs calculated using Cox regression; adjusted for site (KPNC, KPSC), calendar year of entry (2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008), age (18-34, 35-44, 45-54, 55-64, 65-74, 75+), metformin (ever vs. never), Insulin (ever vs. never long, ever vs. never short)

²Insulin use treated as time-varying.

³Glargine users include those who used glargine alone as well as those who had also used NPH

⁴Duration calculated by summing the number of days supply recorded in the pharmacy records for each prescription.

NA = not applicable among prevalent users of NPH at baseline

SUPPLEMENTARY DATA

Supplementary Table 15. Sensitivity Analyses: Hazard ratios (HRs) associated with current use of glargine only versus current use of NPH only among new users of insulin at baseline¹.

Outcome	Insulin	First 2 Years of Follow-up				Greater than 2 Years of Follow-up			
		Events	Pr-years	HR	95% CI	Events	Pr-years	HR	95% CI
Breast	Current use								
	NPH only	102	30,042.9	1.0	Ref	89	22,444.3	1.0	Ref
	Glargine only	18	4,069.8	1.1	0.6-1.8	11	1,620.9	1.6	0.9-3.1
Invasive Breast	Current use								
	NPH only	88	30,042.9	1.0	Ref	71	22,444.3	1.0	Ref
	Glargine only	14	4,069.8	1.0	0.6-1.9	8	1,620.9	1.5	0.7-3.1
Prostate	Current use								
	NPH only	104	31,153.8	1.0	Ref	95	22,247.7	1.0	Ref
	Glargine only	6	5,298.4	0.4	0.2-0.9	6	1,868.6	0.9	0.4-2.1
Colorectal	Current use								
	NPH only	84	61,196.7	1.0	Ref	59	44,692.0	1.0	Ref
	Glargine only	22	9,368.2	1.8	1.1-3.0	5	3,489.4	1.1	0.4-2.8
All Cancer	Current use								
	NPH only	788	61,196.7	1.0	Ref	572	44,692.0	1.0	Ref
	Glargine only	110	9,368.2	1.0	0.8-1.2	48	3,489.4	1.2	0.9-1.7

¹HRs calculated using Cox regression; adjusted for site (KPNC, KPSC), calendar year of entry (2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008),

sex (for colorectal and all cancer s only), age (18-34, 35-44, 45-54, 55-64, 65-74, 75+), metformin use at baseline (yes vs no), short-acting

insulin use at baseline (yes vs no).

Follow-up ended at 6 months after stopping glargine or NPH, switching to another long-acting insulin, any cancer diagnosis, end of membership

or pharmacy benefits, or end of study period (i.e., 12/31/2009), whichever came first.

SUPPLEMENTARY DATA

Supplementary Figure 1. Assembly of study cohort from the Kaiser Permanente Northern California and Southern California health plans.

