

# Insulin glargine use and short-term incidence of malignancies—a population-based follow-up study in Sweden

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## Abstract

**Aims/hypothesis** In the light of a report suggesting that insulin glargine may increase cancer occurrence, the EASD asked us to perform this study.

**Methods** We followed 114,841 individuals who had a prescription dispensed for insulin between 1 July and 31

December 2005. From 1 January 2006 to 31 December 2007, we noted the occurrence of malignancies. Seven different nationwide registers were used to obtain information on insulin exposure, outcome and possible confounders; these were linked using the unique personal identity number assigned to every Swedish resident.

**Results** After adjustment for age and, when appropriate, sex, users of insulin glargine monotherapy (no other types of insulin), compared with users of types of insulin other than insulin glargine, had an RR of 1.99 (95% CI 1.31–3.03) for breast cancer, 0.93 (95% CI 0.61–1.40) for gastrointestinal cancer, 1.27 (95% CI 0.89–1.82) for prostate cancer and 1.07 (95% CI 0.91–1.27) for any type of malignancy. Adjustment for age, smoking, BMI, age at onset of diabetes, age at birth of first child, cardiovascular disease and oestrogen use gave an RR for breast cancer of 1.97 (95% CI 1.29–3.00). The 95% CIs crossed 1.0 for the RR calculated in all analyses of users of insulin glargine in combination with other types of insulin.

**Conclusions/interpretation** In Sweden, during 2006 and 2007, women using insulin glargine monotherapy (no other types of insulin) had an increased incidence rate of breast cancer as compared with women using types of insulin other than insulin glargine. This result may be due to a random fluctuation; the possibilities for examining validity are limited, and no statistically significant results were obtained for any other individual cancer site or for the outcome ‘all malignancies’. No definitive conclusions regarding a possible causal relationship between insulin glargine use and the occurrence of malignancies can be drawn from the results of this study.

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**Keywords** Cancer incidence rate · Diabetes mellitus ·  
Insulin · Insulin glargine

51 **Abbreviations**

53 ATC Anatomical Therapeutic Chemical  
 56 ICD International Classification of Diseases  
 57

58 **Introduction**

59 Since the introduction of non-human insulins, in vitro data  
 60 indicating proliferative and anti-apoptotic activity have  
 61 raised concern [1, 2]. Sweden offers favourable conditions  
 62 for the evaluation of adverse effects of drug use in the  
 63 general population: the Prescribed Drug Register gives  
 64 near-complete coverage of individuals for whom insulin has  
 65 been prescribed, and the Cancer Register contains, by and  
 66 large, all new cases of cancer. A personal identity number,  
 67 unique for each Swedish resident, allows the information  
 68 from different registers on a particular person to be linked  
 69 [3]. In the light of a report suggesting that insulin glargine  
 70 (A21Gly,B31Arg,B32Arg human insulin) may increase  
 71 cancer occurrence [4], the EASD asked us to perform the  
 72 present study. We have investigated the incidence rates of  
 73 breast cancer, gastrointestinal cancer, prostate cancer and  
 74 any type of malignancy associated with the use of insulin  
 75 glargine and compared these with the rates associated with  
 76 the use of other types of insulin.

77 **Methods**

78 We used the unique personal identity number assigned to  
 79 each Swedish resident (about 9 million in total) to link  
 80 together information from seven population-based registers  
 81 (Fig. 1).

82 The Prescribed Drug Register, the Cancer Register, and  
 83 the Causes of Death Register, all maintained by the  
 84 National Board of Health and Welfare were used to obtain  
 85 information on targeted person-time and outcome. We  
 86 retrieved variables reflecting potential confounding factors  
 87 [5] from the Swedish National Diabetes Register (main-  
 88 tained by the local health authorities), the Prescribed Drug  
 89 Register, the National Patient Register [6], and the Medical  
 90 Birth Register [7] (all maintained by the National Board of  
 91 Health and Welfare). Information on educational level was  
 92 extracted from the National Education Register [8], which  
 93 is maintained by Statistics Sweden. By law, local health  
 94 authorities must report all new cases of cancer to the Cancer  
 95 Register, all in-patient information to the National Patient  
 96 Register, all births to the Medical Birth Register, and all  
 97 deaths to the Causes of Death Register [9].

98 The Swedish Prescribed Drug Register contains details  
 99 of all the prescriptions dispensed in Sweden [10]. Updated  
 100 monthly, there are presently around 100 million prescrip-

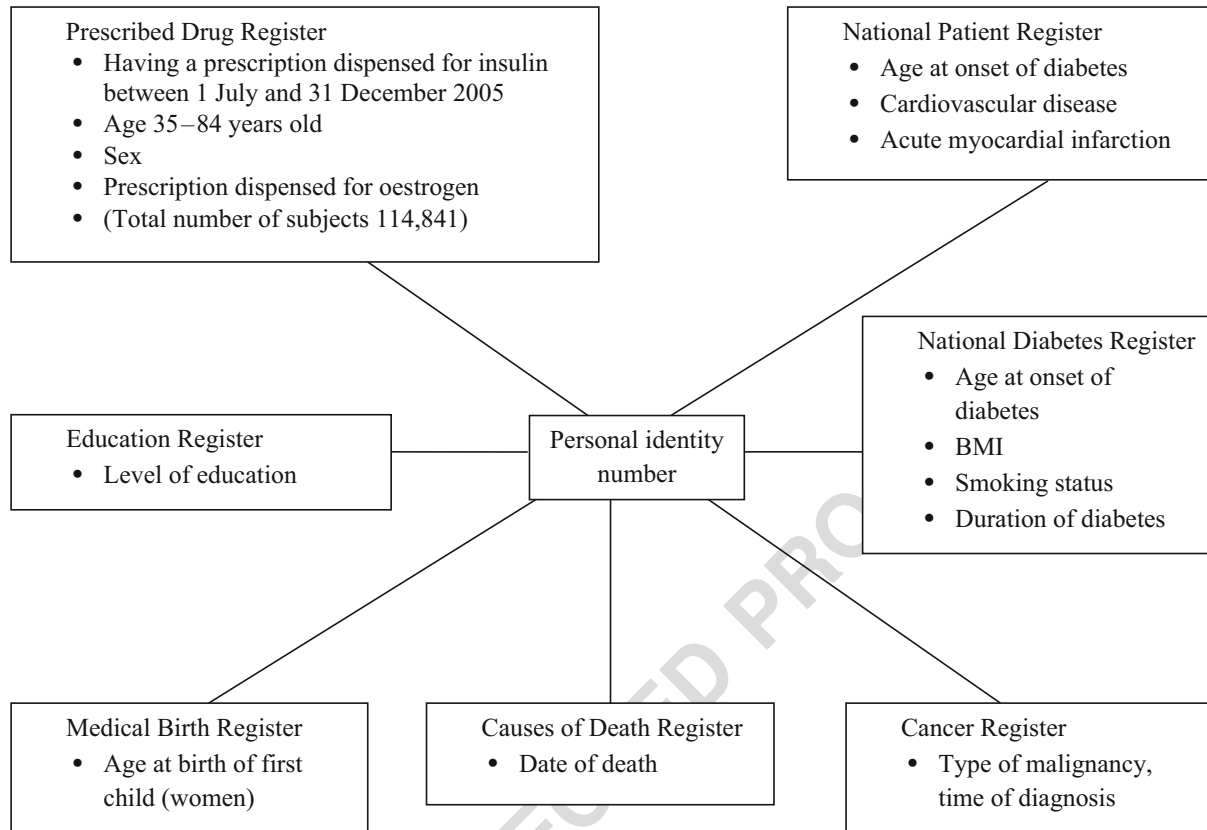
tions dispensed each year. Before 1 July 2005, the personal  
 identity number was not recorded in the register. We  
 therefore had to start recruiting subjects for observation  
 from 1 July 2005.

The Swedish Cancer Register was set up in 1958, and  
 since that time every clinician, pathologist and cytologist in  
 Sweden must notify the National Board of Health and  
 Welfare of each person who has been diagnosed with a new  
 primary malignancy. The Cancer Register includes primary  
 malignancies and certain benign tumours and precancerous  
 lesions [11]. A comparison with death certificates revealed  
 the rate of non-reporting to the National Cancer Registry to  
 be less than 2% during the late 1970s [12], and in a com-  
 parison with the National Patient Register, the rate of non-  
 reporting to the National Cancer Registry was estimated to  
 be 3.7% in 1998 [13].

Launched as a quality assurance register in 1996, the  
 National Diabetes Register includes clinically relevant  
 information [14]. Trained physicians and nurses report the  
 data collected during visits to hospital outpatient clinics and  
 primary healthcare centres via the internet or via clinical  
 record databases. The National Education Register is  
 updated annually with information on the highest formal  
 education achieved.

*Ethical considerations* The Swedish National Board of  
 Health and Welfare is a government agency and may, in  
 accordance with Swedish law, use population-based regis-  
 ters to follow and analyse health and social conditions  
 among the general population. Data were made available to  
 us in such a way that individuals could not be identified.

*Targeted person-time* We have studied all 114,841 indi-  
 viduals who were aged 35–84 years old at the end of  
 2005, had at least one prescription dispensed for insulin  
 (Anatomical Therapeutic Chemical [ATC] code A10A)  
 between 1 July and 31 December 2005, and who were alive  
 at the start of follow-up (1 January 2006). We studied first  
 diagnosis of a primary malignancy as an outcome measure,  
 excluding individuals who received this diagnosis at any  
 time between 1 January 1958 and 31 December 2005. That  
 is, a subject with a record of having been diagnosed with  
 any type of malignancy was excluded for the analyses of  
 outcomes including ‘all malignancies’, and men who had a  
 record of having been diagnosed with prostate cancer before  
 2006 were excluded from the analyses of the outcome  
 ‘prostate cancer’. We followed the subjects from 1 January  
 2006 to 31 December 2007. The number of person-years of  
 follow-up for each individual was from 1 January 2006 to  
 death or loss to follow-up (censorship) or the outcome being  
 analysed or study end. Consequently, the number of  
 observed person-years varies according to the particular type  
 of malignancy studied.



**Fig. 1** The registers used, and the variables retrieved from each register

152 *Categories of insulin use* Information on exposure to insulin  
 153 and analogues was obtained from prescriptions dispensed  
 154 between 1 July and 31 December 2005. Individuals regis-  
 155 tered as having had at least one prescription dispensed for  
 156 insulin glargine (ATC code A10AE04), but no prescriptions  
 157 dispensed for other types of insulin (ATC code A10A) were  
 158 classified as using insulin glargine monotherapy (no other  
 159 types of insulin). Having a prescription dispensed for both  
 160 insulin glargine and another type of insulin, classified the  
 161 individual as a user of insulin glargine and other types of  
 162 insulin. Having a prescription dispensed for insulin but not  
 163 for insulin glargine, classified the individual as a user of  
 164 types of insulin other than insulin glargine.

165 *Outcomes* We studied five malignancy outcomes; death from  
 166 any cause and acute myocardial infarction were also used as  
 167 endpoints. Following the routines for the Cancer Register, the  
 168 outcome ‘all malignancies’ included a carcinoid tumour,  
 169 a granulosa cell tumour, a thymoma, an adamantinoma, a  
 170 chordoma, a transitional cell papilloma of the urinary tract, a  
 171 hormonally active tumour from at least one endocrine gland  
 172 (except the thyroid), an enterochromaffin or a neuroendocrine  
 173 tumour. We also included precancerous lesions, including

gastrointestinal polyps with suspected malignancy, bronchial  
 adenomas, carcinoma in situ of the breast, fibro-adenoma with  
 suspected malignancy, cystosarcoma phyllodes, precancerous  
 endometrial lesions, hydatidiform moles of placental tissue,  
 ovarian cystadenomas of borderline type, histologically  
 benign tumours of the central nervous system and meningio-  
 mas. In situ cases were included with malignant tumours as a  
 second outcome. We defined outcomes for three different  
 anatomical areas: ‘breast cancer’ (International Classification  
 of Diseases, 10th revision [ICD-10] code C50), ‘prostate  
 cancer’ (ICD-10 code C61) and ‘gastrointestinal cancer’  
 (ICD-10: codes C16–C20). For these three areas with only  
 included tumours that were histopathologically classified as  
 adenocarcinoma (WHO/HS/CANC/24.1 histology code 096).

Individuals registered with any type of malignancy  
 between 1 January 1958 and 31 December 2005 were  
 excluded from the analysis when ‘any type of malignancy’  
 was the outcome. When studying breast cancer among women  
 we excluded those who had previously been diagnosed with  
 breast cancer; similar exclusions were made when studying  
 prostate cancer and gastrointestinal cancer. We retrieved the  
 date of death from the Causes of Death register. Subjects who  
 were not registered as dead and who did not have a

197 prescription dispensed for any drug in 2008 were classified  
198 as having been lost to follow-up. The date for loss to follow-  
199 up was set at 90 days after the last date for a dispensed  
200 prescription.

201 *Variables reflecting potential confounding factors* Sex and  
202 age were retrieved from the Prescribed Drug Register. We  
203 obtained data on age at onset of diabetes from the National  
204 Diabetes Register or estimated it from the time for first  
205 admission to hospital care with diabetes as main diagnosis  
206 (ICD-8 code 250; ICD-9 code 250; ICD-10 codes E10–  
207 E14) from data in the Patient Register for 1969 to 2005. An  
208 age at onset of diabetes of less than 30 years, as recorded in  
209 National Diabetes Register (primary choice) or by data  
210 from the Patient Register (secondary choice), defined an  
211 individual as having type 1 diabetes; an age at onset above  
212 30 years defined an individual as having type 2 diabetes;  
213 the absence of information on age at onset defined the indi-  
214 vidual as having missing information on type of diabetes.  
215 The highest BMI reported to the National Diabetes Register  
216 from 2003 to 2005 for each individual was used as the value  
217 for BMI. We retrieved information on smoking habits from  
218 2003 to 2005 from the National Diabetes Register. Anyone  
219 who reported smoking during 2005 was classified as a  
220 current smoker. Anyone who reported not smoking in 2005  
221 but reported smoking in 2003 or 2004 was classified as a  
222 former smoker. Anyone who reported not smoking in 2003,  
223 2004 and 2005 was classified as a non-smoker. A record of a  
224 prescription dispensed for an oestrogen or for metformin in  
225 the Prescribed Drug Register from 1 July to 31 December  
226 2005 defined oestrogen and metformin use, respectively.

227 A record of at least one hospital admission with a main  
228 diagnosis of any cardiovascular disease (ICD-10 codes I00–  
229 I99) in the National Patient Register, during the period 1 July  
230 2004 to 30 June 2005 (i.e. 1 year prior to definition of  
231 exposure), classified the individual as having cardiovascular  
232 disease.

233 Educational level refers to the highest attained educa-  
234 tional level at the end of 2005. Educational level was  
235 classified into the following three categories, representing  
236 distinct levels in the Swedish educational system: (1)  
237 9 years or less of schooling, equivalent to elementary  
238 school or less; (2) 10–12 years of schooling, equivalent to  
239 secondary school; and (3) more than 12 years, equivalent to  
240 university. Age at birth of first child (women only) was  
241 categorised into no children, <30 years, ≥30 years, and  
242 missing information. A large group of women (49%),  
243 mainly the older women in the study population, had  
244 information missing on childbearing.

245 *Statistical methods* As a measure of the relative occurrence  
246 of malignancies, we used the incidence rate ratio. For  
247 example, we calculated the incidence rate of having been

248 diagnosed with any type of malignancy among users of  
249 insulin glargine monotherapy and compared this with the  
250 incidence rate among users of other types of insulin. We  
251 cite this measure of relative occurrence, the incidence rate  
252 ratio, as a relative risk. Poisson regression analyses were  
253 used to evaluate the association between the three groups of  
254 insulin users and malignancy outcome. These models were  
255 fitted with the logarithm of observed person-years as the  
256 offset and they also provided 95% CIs of the incidence rate  
257 ratio. When adjusting for potential confounding factors, we  
258 categorised the numeric variables as presented in Tables 1  
259 and 4, and in order to avoid a substantial reduction of the  
260 number of subjects, we accepted 'missing value' as a single  
261 category in our main analyses. The Genmod procedure in  
262 the SAS statistical software package (SAS Institute, Cary,  
263 NC, USA) was used for the calculations.

## Results

264 Table 1 shows the characteristics of the study subjects at  
265 baseline. Of the 114,841 subjects followed, 5,970 (5.2%)  
267 were classified as users of insulin glargine monotherapy,  
268 20,316 (17.7%) were classified as users of insulin glargine  
269 in combination with other types of insulin, and 88,555  
270 (77.1%) were classified as users of types of insulin other  
271 than insulin glargine. The majority (90%) of users of  
272 insulin glargine monotherapy were classified as having type  
273 2 diabetes or having information missing on type of  
274 diabetes. The same was true of users of types of insulin  
275 other than insulin glargine: a high percentage (89%) were  
276 classified as having type 2 diabetes or having information  
277 missing on type of diabetes. Compared with the other two  
278 groups, the group of users of insulin glargine in combina-  
279 tion with other types of insulin had a lower mean age and a  
280 lower percentage (59%) were classified as having type 2  
281 diabetes or having information missing on type of diabetes.  
282

283 The 95% CIs of the adjusted RRs crossed 1.0 for  
284 malignancy outcomes other than breast cancer (Tables 2  
285 and 3). The RR for breast cancer in women who used  
286 insulin glargine monotherapy compared with those who  
287 used types of insulin other than insulin glargine was 1.91  
288 (95% CI 1.25–2.89) when not adjusted, 1.99 (95% CI 1.31–  
289 3.03) when adjusted for age, and 1.97 (1.30–3.00) when  
290 adjusted for several variables (Table 2). The corresponding  
291 figures for women who used insulin glargine in combina-  
292 tion with other types of insulin compared with those who  
293 used types of insulin other than insulin glargine were  
294 0.92 (0.66–1.29), 1.10 (0.77–1.56) and 1.17 (0.81–1.68)  
295 (Table 3).

296 As a consequence of these results for breast cancer we  
297 then used alternative specifications for the models for breast  
298 cancer, e.g. including age as continuous variable, deleting

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t1.1 **Table 1** Baseline characteristics of the subjects

t1.2	Characteristic	Insulin glargine monotherapy		Insulin glargine and other insulins		Insulins other than insulin glargine		Total	
		n	%	n	%	n	%	n	%
t1.4	Total	5,970		20,316		88,555		114,841	
t1.5	Type of diabetes								
t1.6	Type 1 diabetes	564	9.4	7,903	38.9	9,049	10.2	17,516	15.3
t1.7	Type 2 diabetes	3,750	62.8	10,168	50.0	56,638	64.0	70,556	61.4
t1.8	Missing	1,656	27.7	2,245	11.1	22,868	25.8	26,769	23.3
t1.9	Sex								
t1.10	Male	3,273	54.8	11,427	56.2	50,403	56.9	65,103	56.7
t1.11	Female	2,697	45.2	8,889	43.8	38,152	43.1	49,738	43.3
t1.12	Age at baseline (years)								
t1.13	35-54	1,398	23.4	9,198	45.3	17,144	19.4	27,740	24.2
t1.14	55-64	1,874	31.4	5,922	29.1	22,697	25.6	30,493	26.6
t1.15	65-74	1,489	24.9	3,557	17.5	25,668	29.0	30,714	26.7
t1.16	75-84	1,209	20.3	1,639	8.1	23,046	26.0	25,894	22.5
t1.17	Age at onset of diabetes (years)								
t1.18	0-14	236	4.0	3,386	16.7	3,602	4.1	7,224	6.3
t1.19	15-29	328	5.5	4,517	22.2	5,447	6.2	10,292	9.0
t1.20	30-44	937	15.7	5,125	25.2	13,412	15.1	19,474	17.0
t1.21	45-54	1,206	20.2	2,914	14.5	17,272	19.5	21,419	18.7
t1.22	55-64	1,057	17.7	1,586	7.8	16,488	18.6	19,131	16.7
t1.23	65-84	550	9.2	516	2.5	9,466	10.7	10,532	9.2
t1.24	Missing	1,656	27.7	2,245	11.1	22,868	25.8	26,769	23.3
t1.25	BMI (kg/m <sup>2</sup> )								
t1.26	15≤BMI<25	660	11.1	5,080	25.0	9,154	10.3	14,894	13.0
t1.27	25≤BMI<30	1,094	18.3	5,626	27.7	16,878	19.1	23,598	20.5
t1.28	30≤BMI<35	686	11.5	2,242	11.0	11,320	12.8	14,248	12.4
t1.29	≥35	374	6.3	821	4.0	5,898	6.7	7,093	6.2
t1.30	Missing	3,156	52.9	6,547	32.2	45,305	51.2	55,008	47.9
t1.31	Smoking								
t1.32	Non-smoker <sup>a</sup>	2,287	38.3	11,697	57.6	36,891	41.7	50,875	44.3
t1.33	Former smoker <sup>b</sup>	223	3.7	953	4.7	2,825	3.2	4,001	3.5
t1.34	Current smoker <sup>c</sup>	346	5.8	1,515	7.5	4,430	5.0	6,291	5.5
t1.35	Missing	3,114	52.2	6,151	30.3	44,409	50.1	53,674	46.7

<sup>a</sup> Defined as a person who reported not smoking in 2003, 2004 and 2005

<sup>b</sup> Defined as a person who reported smoking in 2003 or 2004, but reported not smoking in 2005

<sup>c</sup> Defined as a person who reported smoking in 2005

299 observations with missing values and replacing the  
 300 assumption of Poisson distribution with negative binomial  
 301 distribution. None of these alternative specifications had a  
 302 substantial effect on the results. We also performed  
 303 additional analyses restricted to women. The demographic  
 304 data for those women who were not diagnosed with breast  
 305 cancer from 1958 to 2005 are shown in Table 4; a pattern  
 306 similar to that shown in Table 1 can be seen. We examined  
 307 all available variables that may reflect one (or several) risk  
 308 factor for breast cancer. The adjusted RRs varied between

1.96 and 2.00 for women who used insulin glargine  
 monotherapy compared with those who used types of  
 insulin other than insulin glargine (Table 5).

Taking an extra latency period of 1 year into account,  
 thereby starting follow-up on 1 January 2007, yielded a  
 somewhat higher RR for users of insulin glargine mono-  
 therapy (2.22, 95% CI 1.24-3.99). After extending the  
 exposure period to 1 year, from 1 July 2005 to 30 June  
 2006, and starting follow-up on 1 July 2006, we found that,  
 among users of insulin glargine monotherapy, the RR of

**Table 2** Incidence rate and incidence rate ratio for cancer for users of insulin glargine monotherapy compared with users of types of insulin other than insulin glargine

Cancer outcome	Types of insulin other than insulin glargine (reference category)			Insulin glargine monotherapy			Incidence rate ratio <sup>a</sup> (95% CI)	
	No. of cases	Person-years	Incidence rate (per 1,000 person-years)	No. of cases	Person-years	Incidence rate (per 1,000 person-years)	Unadjusted	Adjusted for Age and, when appropriate, sex
t2.3	2,199	148,804	14.8	149	10,323	14.4	0.98 (0.83–1.15)	1.07 (0.91–1.27)
t2.4	2,353	144,499	16.3	156	10,009	15.6	0.96 (0.81–1.13)	1.05 (0.90–1.24)
t2.5	183	69,358	2.6	25	4,974	5.0	1.91 (1.25–2.89)	1.99 (1.31–3.03)
t2.6	432	91,845	4.7	32	6,037	5.3	1.13 (0.79–1.61)	1.27 (0.89–1.82)
t2.7	430	165,152	2.6	24	11,273	2.1	0.82 (0.54–1.23)	0.93 (0.61–1.40)

<sup>a</sup> Incidence rate ratio is referred to as the RR in the text

<sup>b</sup> Adjusted for age, sex, BMI, smoking, age at onset of diabetes, and cardiovascular disease

<sup>c</sup> Adjusted for age, BMI, smoking, age at onset of diabetes, cardiovascular disease, and age at birth of first child

<sup>d</sup> Adjusted for age, BMI, smoking, age at onset of diabetes, and cardiovascular disease

**Table 3** Incidence rate and incidence rate ratio for cancer for users of insulin glargine in combination with other insulins compared with users of types of insulin other than insulin glargine

Cancer outcome	Types of insulin other than insulin glargine (reference category)			Insulin glargine in combination with other insulins			Incidence rate ratio <sup>a</sup> (95% CI)	
	No. of cases	Person-years	Incidence rate (per 1,000 person-years)	No. of cases	Person-years	Incidence rate (per 1,000 person-years)	Unadjusted	Adjusted for Age and sex
t3.1	2,199	148,804	14.8	341	36,892	9.2	0.63 (0.56–0.70)	0.95 (0.85–1.07)
t3.2	2,353	144,499	16.3	360	35,902	10.0	0.62 (0.55–0.69)	0.94 (0.84–1.06)
t3.3	183	69,358	2.6	41	16,882	2.4	0.92 (0.66–1.29)	1.10 (0.77–1.56)
t3.4	432	91,845	4.7	58	21,862	2.7	0.56 (0.43–0.74)	0.98 (0.74–1.30)
t3.5	430	165,152	2.6	50	39,305	1.3	0.49 (0.36–0.65)	0.80 (0.59–1.08)

<sup>a</sup> Incidence rate ratio is referred to as the RR in the text

<sup>b</sup> Adjusted for age, sex, BMI, smoking, age at onset of diabetes, and cardiovascular disease

<sup>c</sup> Adjusted for age, BMI, smoking, age at onset of diabetes, cardiovascular disease, and age at birth of first child

<sup>d</sup> Adjusted for age, BMI, smoking, age at onset of diabetes, and cardiovascular disease

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t4.1 **Table 4** Baseline characteristics of women in the analyses of breast cancer

t4.2	Characteristic	Insulin use during 2005						Total	
		Insulin glargine monotherapy		Insulin glargine in combination with other insulins		Types of insulin other than insulin glargine		n	%
t4.3		n	%	n	%	n	%		
t4.4	Total	2,595		8,649		36,532		47,776	100.0
t4.5	Type of diabetes								
t4.6	Type 1 diabetes	298	11.5	3,578	41.4	4,081	11.2	7,957	16.7
t4.7	Type 2 diabetes	1,566	60.3	4,148	48.0	22,831	62.5	28,545	59.7
t4.8	Missing	731	28.2	923	10.7	9,620	26.3	11,274	23.6
t4.9	Age at baseline (years)								
t4.10	35–54	646	24.9	3,856	44.6	6,735	18.4	11,237	23.5
t4.11	55–64	691	26.6	2,371	27.4	8,089	22.1	11,151	23.3
t4.12	65–74	633	24.4	1,581	18.3	10,416	28.5	12,630	26.4
t4.13	75–84	625	24.1	841	9.7	11,292	30.9	12,758	26.7
t4.14	Age at onset of diabetes (years)								
t4.15	0–14	136	5.2	1,678	19.4	1,772	4.9	3,586	7.5
t4.16	15–29	162	6.2	1,900	22.0	2,309	6.3	4,371	9.1
t4.17	30–44	397	15.3	1,937	22.4	4,939	13.5	7,273	15.2
t4.18	45–54	438	16.9	1,166	13.5	6,444	17.6	8,048	16.8
t4.19	55–64	452	17.4	749	8.7	6,934	19.0	8,135	17.0
t4.20	65–84	279	10.8	296	3.4	4,514	12.4	5,089	10.7
t4.21	Missing	731	28.2	923	10.7	9,620	26.3	11,274	23.6
t4.22	BMI (kg/m <sup>2</sup> )								
t4.23	15 ≤ BMI < 25	321	12.4	2,482	28.7	3,931	10.8	6,734	14.1
t4.24	25 ≤ BMI < 30	422	16.3	1,972	22.8	5,728	15.7	8,122	17.0
t4.25	30 ≤ BMI < 35	275	10.6	981	11.3	4,703	12.9	5,959	12.5
t4.26	≥ 35	186	7.2	435	5.0	3,189	8.7	3,810	8.0
t4.27	Missing	1,391	53.6	2,779	32.1	18,981	52.0	23,151	48.5
t4.28	Smoking								
t4.29	Non-smoker <sup>a</sup>	1,010	38.9	4,928	57.0	15,183	41.6	21,121	44.2
t4.30	Former smoker <sup>b</sup>	88	3.4	422	4.9	1,103	3.0	1,613	3.4
t4.31	Current smoker <sup>c</sup>	148	5.7	735	8.5	1,763	4.8	2,646	5.5
t4.32	Missing	1,349	52.0	2,564	29.6	18,483	50.6	22,396	46.9
t4.33	Education								
t4.34	Elementary school	865	33.3	2,218	25.6	14,229	38.9	17,312	36.2
t4.35	Secondary school	953	36.7	3,955	45.7	11,969	32.8	16,877	35.3
t4.36	University	404	15.6	2,112	24.4	4,189	11.5	6,705	14.0
t4.37	Missing	373	14.4	364	4.2	6,145	16.8	6,882	14.4
t4.38	Age at birth of first child								
t4.39	No children	585	22.5	2,267	26.2	7,053	19.3	9,905	20.7
t4.40	< 30 years	687	26.5	3,370	39.0	7,448	20.4	11,505	24.1
t4.41	≥ 30 years	155	6.0	864	10.0	1,805	4.9	2,824	5.9
t4.42	Missing	1,168	45.0	2,148	24.8	20,226	55.4	23,542	49.3
t4.43	Oestrogen use								
t4.44	Yes	375	14.5	1,222	14.1	5,093	13.9	6,690	14.0
t4.45	No	2,220	85.5	7,427	85.9	31,439	86.1	41,086	86.0
t4.46	Metformin use								
t4.47	Yes	1,278	49.2	1,237	14.3	14,214	38.9	16,729	35.0
t4.48	No	1,317	50.8	7,412	85.7	22,318	61.1	31,047	65.0

<sup>a</sup> Defined as a person who reported not smoking in 2003, 2004 and 2005

<sup>b</sup> Defined as a person who reported smoking in 2003 or 2004, but reported not smoking in 2005

<sup>c</sup> Defined as a person who reported smoking in 2005

t5.1	Table 5 Incidence rate ratio for breast cancer among women using insulin glargine monotherapy or using insulin glargine in combination with other types of insulin, compared with women using types of insulin other than insulin glargine	Model	Incidence rate ratio <sup>a</sup> (95% CI)		t5.2
			Insulin glargine monotherapy	Insulin glargine in combination with other types of insulin	
		Unadjusted	1.91 (1.25–2.89)	0.92 (0.66–1.29)	t5.4
		Adjusted for			t5.5
		Age	1.99 (1.31–3.03)	1.10 (0.77–1.56)	t5.6
		Age and metformin	1.98 (1.30–3.01)	1.11 (0.78–1.59)	t5.7
		Age and oestrogen	1.99 (1.31–3.02)	1.08 (0.76–1.54)	t5.8
		Age and BMI	1.97 (1.31–3.00)	1.16 (0.81–1.65)	t5.9
		Age and smoking	1.97 (1.31–3.00)	1.16 (0.81–1.65)	t5.10
		Age and age at onset of diabetes	1.96 (1.29–2.97)	1.16 (0.81–1.65)	t5.11
		Age and cardiovascular disease	2.00 (1.31–3.04)	1.10 (0.77–1.56)	t5.12
		Age and age at birth of first child	2.00 (1.31–3.04)	1.11 (0.77–1.56)	t5.13
		Multiple variables <sup>b</sup>	1.97 (1.29–3.00)	1.15 (0.80–1.65)	t5.14
		Restricted to age 35–79 years and adjusted for			t5.15
		Multiple variables <sup>b</sup>	1.98 (1.25–3.13)	1.14 (0.78–1.67)	t5.16
		Multiple variables <sup>b</sup> and educational level	1.98 (1.25–3.13)	1.14 (0.78–1.67)	t5.17

<sup>a</sup> Incidence rate ratio is referred to as the RR in the text

<sup>b</sup> Age, age at birth of first child, age at onset of diabetes, BMI, cardiovascular disease, oestrogen use and smoking

319 breast cancer was 2.14 (95% 1.24–3.71) for women with  
 320 three or more prescriptions dispensed for insulin glargine  
 321 and 1.53 (0.49–4.79) for women with one to two prescrip-  
 322 tions dispensed, compared with those with no prescrip-  
 323 tions dispensed for insulin glargine. We saw no statistically  
 324 significant increase in incidence rate with increasing number  
 325 of daily defined doses of insulin glargine (data not shown).

326 When restricting the analysis to those with type 1  
 327 diabetes or those with type 2 diabetes, a statistically  
 328 significant difference in breast cancer occurrence between  
 329 users of insulin glargine monotherapy and users of types of  
 330 insulin other than insulin glargine was seen for both types  
 331 of diabetes (data not shown). Further analysis of the RR for  
 332 each type of diabetes was not possible because of the small  
 333 number of cases. The incidence rate of breast cancer was  
 334 low before age 55; it was therefore not possible to study  
 335 pre- and postmenopausal breast cancer. To obtain a measure  
 336 of breast cancer occurrence after having used insulin  
 337 glargine, irrespective of whether alone or together with  
 338 other types of insulin, we combined the two groups of  
 339 insulin glargine users and adjusted the RR for age, age at  
 340 birth of first child, age at onset of diabetes, BMI, having  
 341 had cardiovascular disease, oestrogen use and smoking.  
 342 This gave an RR of 1.40 (1.04–1.89).

343 When we studied acute myocardial infarction as an  
 344 outcome and adjusted for age, age at onset of diabetes, BMI  
 345 and smoking, we obtained an RR of 0.77 (0.59–1.00) for  
 346 female users of insulin glargine monotherapy, and 0.88  
 347 (0.74–10.05) for female users of insulin glargine together  
 348 with other types of insulin, compared with female users of  
 349 types of insulin other than insulin glargine. When investi-  
 350 gating mortality, we adjusted for age, age at onset of

diabetes, BMI, smoking and having had cardiovascular  
 disease. Women using insulin glargine monotherapy had a  
 mortality ratio of 0.83 (95% CI 0.71–0.96) and female users  
 of insulin glargine together with other types of insulin had a  
 mortality ratio of 0.87 (0.77–0.97), compared with female  
 users of types of insulin other than insulin glargine.

### Discussion

We found that the incidence rates for gastrointestinal  
 cancer, prostate cancer, and any type of malignancy among  
 users of insulin glargine were similar to the incidence rates  
 among users of other types of insulin. In Sweden, during  
 2006 and 2007, users of insulin glargine monotherapy had a  
 higher incidence rate of breast cancer than users of types of  
 insulin other than insulin glargine.

We cannot rule out that the increased incidence rate for  
 breast cancer in Sweden during 2006 and 2007 among  
 users of insulin glargine monotherapy, compared with users  
 of other types of insulin, was the result of random  
 fluctuation; statistical significance does not exclude this  
 possibility. When examining problems with validity, we are  
 limited to the information available in the registers; we  
 cannot rule out validity problems for which we have no  
 data. Specifically, we lack data on important possible  
 confounding factors and, for some, we depend on data  
 from the National Diabetes Register, which only covers  
 about half of the individuals we study. All risk factors for  
 breast cancer may confound the results we obtained; risk  
 factors explaining a large proportion of the variation in the  
 incidence rate for breast cancer in Sweden are more likely

380 to confound the association than risk factors explaining  
381 only a small percentage.

382 Adjusting for available variables changed the RR to such  
383 a small degree that we can exclude significant confounding  
384 [5] by risk factors for breast cancer such as age at birth of  
385 first child [15], BMI [16], educational level [17], metformin  
386 intake [18] and oestrogen intake [19]. We do not know to  
387 what extent available variables reflect alcohol intake [20,  
388 21], food intake [22] or health consciousness, and we do  
389 not have any information on genetic predisposition to breast  
390 cancer (e.g. presence of a mutation in *BRCA1* [23–25] or  
391 *BRCA2* [26, 27]).

392 To prevent the development of cancer having any  
393 influence on selection for observation of cancer occurrence  
394 ('reversed causality'), we performed a fixed-cohort analy-  
395 sis, classifying individuals according to drug prescriptions  
396 dispensed in 2005. Some individuals registered as having a  
397 drug prescription dispensed for other types of insulin may  
398 certainly have used insulin glargine before 2005 or during  
399 the observation period during 2006 and 2007. This error  
400 often causes a non-differential misclassification of expo-  
401 sure, which shifts the RR towards 1.0 [28]. In other words,  
402 the uncertainty surrounding the extent to which a registered  
403 prescription dispensed for insulin glargine reflects real-life  
404 use of insulin glargine limits our ability to detect the true  
405 effect on the occurrence of malignancies. This limitation  
406 does not, however, as a rule, produce a spurious result  
407 indicating an effect. Thus, if we had been able to eliminate  
408 this inaccuracy, allowing us to only study the true users of  
409 insulin glargine with respect to the development of  
410 malignancies over the relevant time period, we would  
411 probably have obtained an age-adjusted RR higher than the  
412 1.99 we obtained for breast cancer for users of insulin  
413 glargine monotherapy. The available information indicates  
414 that loss to follow-up was small and did not differ between  
415 the different treatment groups. We did not find any  
416 indication of reversed causality, that is, of the presence of  
417 cancer having influenced the likelihood of using, or not  
418 using, insulin glargine. The mortality rate and the incidence  
419 rate of acute myocardial infarction were lower for users of  
420 insulin glargine monotherapy than for users of other types  
421 of insulin but not insulin glargine; we have no indication  
422 that users of insulin glargine monotherapy had a higher rate  
423 of morbidity than the comparison group.

424 Duration from the start of exposure of industrial agents  
425 to an excess risk of cancer is usually 10–25 years. Among  
426 users of the drug chlornaphazine, an agent used to treat  
427 polycytemia verae, an increased risk of bladder cancer was  
428 observed as early as 3–5 years after treatment initiation  
429 [29, 30]. Chlornaphazine resembles the extremely strong and  
430 remarkably species-unspecific bladder cancer carcinogen  $\beta$ -  
431 naphthylamine. We are not aware of any documentation of an  
432 increased incidence of cancer the year after initiation of

treatment with a specific drug. Insulin glargine appeared on 433  
the Swedish market in 2003, and we do not know the 434  
percentage of users of insulin glargine who started using the 435  
drug in that year. Nevertheless, the short duration from 436  
the start of insulin glargine use to the increased incidence rate 437  
for breast cancer suggests that our results could be due to 438  
random fluctuation. 439

440 We have no evidence of whether the difference in inci-  
441 dence rate for breast cancer among users of insulin glargine  
442 monotherapy, compared with users of insulin glargine  
443 together with other types of insulin, is caused by random  
444 fluctuations, interaction between insulin glargine and another  
445 insulin, or the presence of an as-yet-unidentified effect-  
446 modifying factor in the insulin glargine monotherapy group.  
447 Any suggestion of an explanation would be pure speculation.  
448 The group of users of insulin glargine in combination with  
449 other types of insulin had a lower mean age and had more  
450 often type 1 diabetes than the other two groups.

451 Weinstein and co-workers demonstrated that insulin  
452 glargine stimulates the proliferation of cultured colorectal,  
453 prostate and breast cancer cells [2]. Epidemiological studies  
454 link circulating IGF-I concentrations to the incidence of  
455 breast, prostate and colorectal cancer [31–33]. Insulin  
456 glargine may have a similar mechanism of action to IGF-  
457 I. Thus, before the study, we expected that an increased  
458 incidence rate of breast cancer, if present, would occur in  
459 parallel with an increased incidence rate of gastrointestinal  
460 and prostate cancer. We found no statistically significant  
461 results for prostate or gastrointestinal cancer, which, again,  
462 strengthens the interpretation that the breast cancer results  
463 were due to random fluctuation.

464 Data from other settings are needed before any true  
465 effects of the incidence of malignancies related to insulin  
466 glargine can be evaluated with a high level of confidence.  
467 When more evidence becomes available, the absolute  
468 increase in incidence, if any, must be weighed against the  
469 beneficial effects, as well as other adverse effects, of using  
470 insulin glargine compared with other types of insulin.

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