ARTICLE

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

J. M. Jonasson · R. Ljung · M. Talbäck · B. Haglund · S. Gudbjörnsdòttir · G. Steineck

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 alone (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 alone (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.

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

J. M. Jonasson · G. Steineck (✉)
Division of Clinical Cancer Epidemiology,
Department of Oncology, Onkologiskt Centrum,
Sahlgrenska Academy,
41345 Gothenburg, Sweden
e-mail: Gunnar.Steineck@gu.se

J. M. Jonasson · G. Steineck
Division of Clinical Cancer Epidemiology,
Department of Oncology-Pathology, Karolinska Institutet,
Stockholm, Sweden

R. Ljung · M. Talbäck · B. Haglund
The National Board of Health and Welfare,
Stockholm, Sweden

R. Ljung
Equity and Health Policy, Department of Public Health Sciences,
Karolinska Institutet,
Stockholm, Sweden

R. Ljung
Upper Gastrointestinal Research,
Department of Molecular Medicine and Surgery,
Karolinska Institutet,
Stockholm, Sweden

S. Gudbjörnsdòttir
Diabetes Centre, Sahlgrenska University Hospital,
Gothenburg, Sweden

S. Gudbjörnsdòttir
Nordic School of Public Health,
Gothenburg, Sweden

Abbreviations

ATC   Anatomical Therapeutic Chemical
ICD   International Classification of Diseases

Introduction

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

Methods

We used the unique personal identity number assigned to each Swedish resident (about 9 million in total) to link together information from seven population-based registers (Fig. 1) [3].

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

The Swedish Prescribed Drug Register contains details of all the prescriptions dispensed in Sweden [10]. Updated 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 comparison 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 registers 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 individuals 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 from 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.
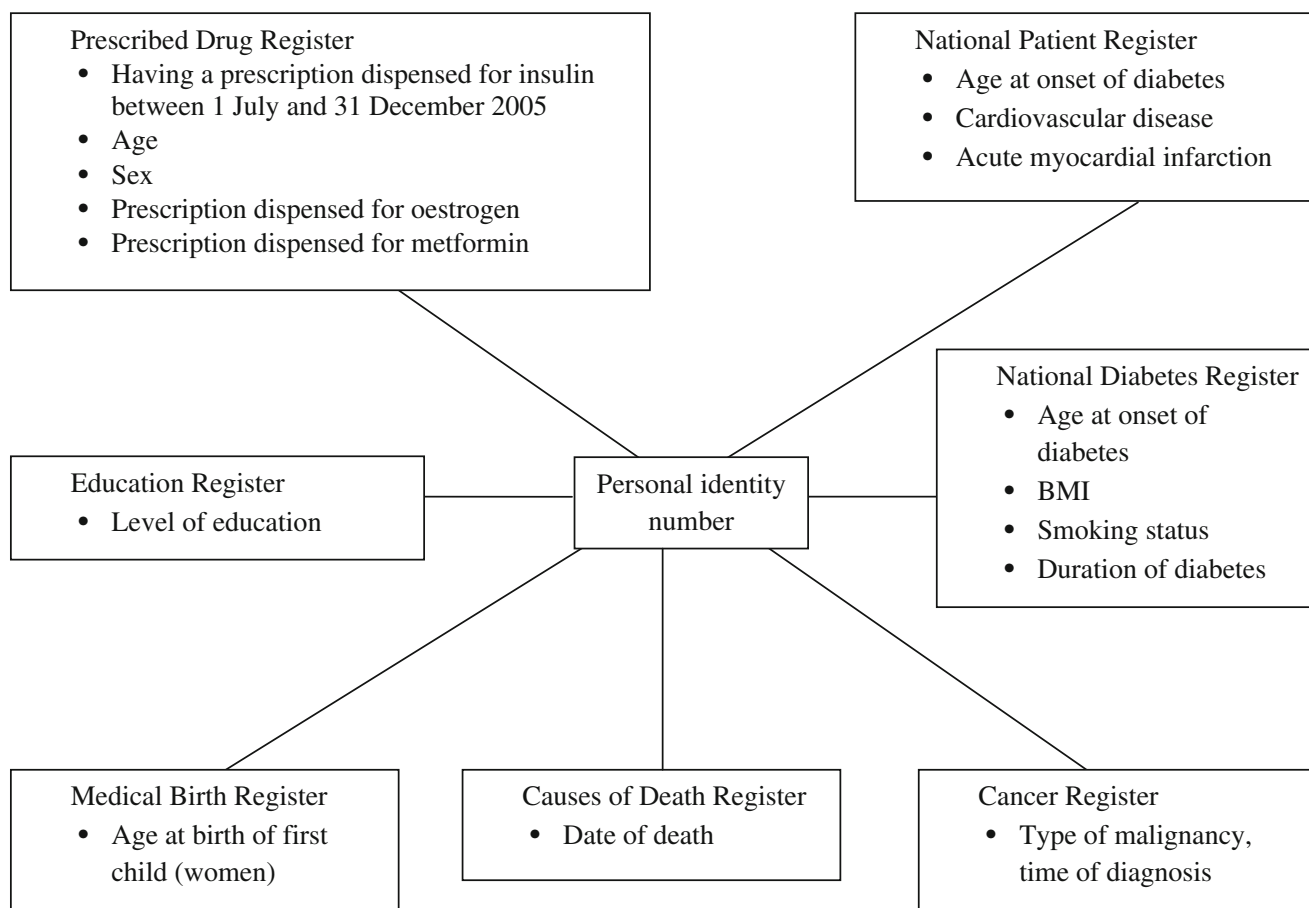
Fig. 1 The registers used, and the variables retrieved from each register

Categories of insulin use Information on exposure to insulin and analogues was obtained from prescriptions dispensed between 1 July and 31 December 2005. Individuals registered as having had at least one prescription dispensed for insulin glargine (ATC code A10AE04), but no prescriptions dispensed for other types of insulin (ATC code A10A) were classified as using insulin glargine alone (no other types of insulin). Having a prescription dispensed for both insulin glargine and another type of insulin classified the individual as a user of insulin glargine and other types of insulin. Having a prescription dispensed for insulin but not for insulin glargine, classified the individual as a user of types of insulin other than insulin glargine.

Outcomes We studied five malignancy outcomes; death from any cause and acute myocardial infarction were also used as endpoints. Following the routines for the Cancer Register, the outcome 'all malignancies' included a carcinoid tumour, a granulosa cell tumour, a thymoma, an adamantinoma, a chordoma, a transitional cell papilloma of the urinary tract, a hormonally active tumour from at least one endocrine gland (except the thyroid), an enterochromaffin or a neuroendocrine 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, adenoma phyllodes, precancerous endometrial lesions, hydatidiform moles of placental tissue, ovarian cystadenomas of borderline type, histologically benign tumours of the central nervous system and meningomas. 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 we 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

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

Variables reflecting potential confounding factors Sex and age were retrieved from the Prescribed Drug Register. We obtained data on age at onset of diabetes from the National Diabetes Register or estimated it from the time for first admission to hospital care with diabetes as the main diagnosis (ICD-8 code 250; ICD-9 code 250; ICD-10 codes E10–E14) from data in the Patient Register for 1969 to 2005. An age at onset of diabetes of less than 30 years, as recorded in the National Diabetes Register (primary choice) or by data from the Patient Register (secondary choice), defined an individual as having type 1 diabetes; an age at onset above 30 years defined an individual as having type 2 diabetes; the absence of information on age at onset defined the individual as having missing information on type of diabetes. The highest BMI reported to the National Diabetes Register from 2003 to 2005 for each individual was used as the value for BMI. We retrieved information on smoking habits from 2003 to 2005 from the National Diabetes Register. Anyone who reported smoking during 2005 was classified as a current smoker. Anyone who reported not smoking in 2005 but reported smoking in 2003 or 2004 was classified as a former smoker. Anyone who reported not smoking in 2003, 2004 and 2005 was classified as a non-smoker. A record of a prescription dispensed for an oestrogen or for metformin in the Prescribed Drug Register from 1 July to 31 December 2005 defined oestrogen and metformin use, respectively.

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

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

Statistical methods As a measure of the relative occurrence of malignancies, we used the incidence rate ratio. For example, we calculated the incidence rate of having been diagnosed with any type of malignancy among users of insulin glargine alone and compared this with the incidence rate among users of other types of insulin. We cite this measure of relative occurrence, the incidence rate ratio, as a relative risk. Poisson regression analyses were used to evaluate the association between the three groups of insulin users and malignancy outcome. These models were fitted with the logarithm of observed person-years as the offset and they also provided 95% CIs of the incidence rate ratio. When adjusting for potential confounding factors, we categorised the numeric variables as presented in Tables 1 and 4, and in order to avoid a substantial reduction of the number of subjects, we accepted 'missing value' as a single category in our main analyses. The Genmod procedure in the SAS statistical software package (SAS Institute, Cary, NC, USA) was used for the calculations.

Results

Table 1 shows the characteristics of the study subjects at baseline. Of the 114,841 subjects followed, 5,970 (5.2%) were classified as users of insulin glargine alone, 20,316 (17.7%) were classified as users of insulin glargine in combination with other types of insulin, and 88,555 (77.1%) were classified as users of types of insulin other than insulin glargine. The majority (90.6%) of users of insulin glargine alone were classified as having type 2 diabetes or having information missing on type of diabetes. The same was true of users of types of insulin other than insulin glargine: a high percentage (89.8%) were classified as having type 2 diabetes or having information missing on type of diabetes. Compared with the other two groups, the group of users of insulin glargine in combination with other types of insulin had a lower mean age and a lower percentage (61.1%) were classified as having type 2 diabetes or having information missing on type of diabetes.

The 95% CIs of the adjusted RRs included 1.0 for malignancy outcomes other than breast cancer (Tables 2 and 3). The RR for breast cancer in women who used insulin glargine alone compared with those who used types of insulin other than insulin glargine was 1.91 (95% CI 1.25–2.89) when not adjusted, 1.99 (95% CI 1.31–3.03) when adjusted for age, and 1.97 (1.30–3.00) when adjusted for several variables (Table 2). The corresponding figures for women who used insulin glargine in combination with other types of insulin compared with those who used types of insulin other than insulin glargine were 0.92 (0.66–1.29), 1.10 (0.77–1.56) and 1.17 (0.81–1.68) (Table 3).

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

Table 1 Baseline characteristics of the subjects

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

[a] Defined as a person who reported not smoking in 2003, 2004 and 2005

[b] Defined as a person who reported smoking in 2003 or 2004, but reported not smoking in 2005

[c] Defined as a person who reported smoking in 2005

observations with missing values and replacing the assumption of Poisson distribution with negative binominal distribution. None of these alternative specifications had a substantial effect on the results. We also performed additional analyses restricted to women. The demographic data for those women who were not diagnosed with breast cancer from 1958 to 2005 are shown in Table 4; a pattern similar to that shown in Table 1 can be seen. We examined all available variables that may reflect one (or several) risk factor for breast cancer. The adjusted RRs varied between 1.96 and 2.00 for women using insulin glargine alone compared with those using 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 alone (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 alone, the RR of breast cancer was

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

Cancer outcome	Types of insulin other than insulin glargine (reference category)			Insulin glargine alone			Incidence rate ratio[a] (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	See footnote
All malignant tumours	2,199	148,804	14.8	149	10,323	14.4	0.98 (0.83–1.15)	1.07 (0.91–1.27)	1.06 (0.90–1.25)[b]
All malignant tumours and in situ tumours	2,353	144,499	16.3	156	10,009	15.6	0.96 (0.81–1.13)	1.05 (0.90–1.24)	1.04 (0.88–1.22)[b]
Breast cancer (women)	183	69,358	2.6	25	4,974	5.0	1.91 (1.25–2.89)	1.99 (1.31–3.03)	1.97 (1.30–3.00)[c]
Prostate cancer	432	91,845	4.7	32	6,037	5.3	1.13 (0.79–1.61)	1.27 (0.89–1.82)	1.26 (0.88–1.80)[d]
Gastrointestinal cancer	430	165,152	2.6	24	11,273	2.1	0.82 (0.54–1.23)	0.93 (0.61–1.40)	0.91 (0.61–1.38)[b]

[a] Incidence rate ratio is referred to as the RR in the text

[b] Adjusted for age, sex, BMI, smoking, age at onset of diabetes, and cardiovascular disease

[c] Adjusted for age, BMI, smoking, age at onset of diabetes, cardiovascular disease, and age at birth of first child

[d] 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[a] (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	See footnote
All malignant tumours	2,199	148,804	14.8	341	36,892	9.2	0.63 (0.56–0.70)	0.95 (0.85–1.07)	1.02 (0.91–1.15)[b]
All malignant tumours and in situ tumours	2,353	144,499	16.3	360	35,902	10.0	0.62 (0.55–0.69)	0.94 (0.84–1.06)	1.00 (0.89–1.13)[b]
Breast cancer (women)	183	69,358	2.6	41	16,882	2.4	0.92 (0.66–1.29)	1.10 (0.77–1.56)	1.17 (0.81–1.68)[c]
Prostate cancer	432	91,845	4.7	58	21,862	2.7	0.56 (0.43–0.74)	0.98 (0.74–1.30)	1.05 (0.79–1.40)[d]
Gastrointestinal cancer	430	165,152	2.6	50	39,305	1.3	0.49 (0.36–0.65)	0.80 (0.59–1.08)	0.82 (0.61–1.12)[b]

[a] Incidence rate ratio is referred to as the RR in the text

[b] Adjusted for age, sex, BMI, smoking, age at onset of diabetes, and cardiovascular disease

[c] Adjusted for age, BMI, smoking, age at onset of diabetes, cardiovascular disease, and age at birth of first child

[d] Adjusted for age, BMI, smoking, age at onset of diabetes, and cardiovascular disease

Table 4 Baseline characteristics of women in the analyses of breast cancer

Characteristic	Insulin use during 2005						Total	
	Insulin glargine alone		Insulin glargine in combination with other insulins		Types of insulin other than insulin glargine			
	n	%	n	%	n	%	n	%
Total	2,595		8,649		36,532		47,776	100.0
Type of diabetes								
Type 1 diabetes	298	11.5	3,578	41.4	4,081	11.2	7,957	16.7
Type 2 diabetes	1,566	60.3	4,148	48.0	22,831	62.5	28,545	59.7
Missing	731	28.2	923	10.7	9,620	26.3	11,274	23.6
Age at baseline (years)								
35–54	646	24.9	3,856	44.6	6,735	18.4	11,237	23.5
55–64	691	26.6	2,371	27.4	8,089	22.1	11,151	23.3
65–74	633	24.4	1,581	18.3	10,416	28.5	12,630	26.4
75–84	625	24.1	841	9.7	11,292	30.9	12,758	26.7
Age at onset of diabetes (years)								
0–14	136	5.2	1,678	19.4	1,772	4.9	3,586	7.5
15–29	162	6.2	1,900	22.0	2,309	6.3	4,371	9.1
30–44	397	15.3	1,937	22.4	4,939	13.5	7,273	15.2
45–54	438	16.9	1,166	13.5	6,444	17.6	8,048	16.8
55–64	452	17.4	749	8.7	6,934	19.0	8,135	17.0
65–84	279	10.8	296	3.4	4,514	12.4	5,089	10.7
Missing	731	28.2	923	10.7	9,620	26.3	11,274	23.6
BMI (kg/m^2)								
15≤ BMI <25	321	12.4	2,482	28.7	3,931	10.8	6,734	14.1
25≤ BMI <30	422	16.3	1,972	22.8	5,728	15.7	8,122	17.0
30≤ BMI <35	275	10.6	981	11.3	4,703	12.9	5,959	12.5
35≤ BMI ≤50	186	7.2	435	5.0	3,189	8.7	3,810	8.0
Missing	1,391	53.6	2,779	32.1	18,981	52.0	23,151	48.5
Smoking								
Non-smoker[a]	1,010	38.9	4,928	57.0	15,183	41.6	21,121	44.2
Former smoker[b]	88	3.4	422	4.9	1,103	3.0	1,613	3.4
Current smoker[c]	148	5.7	735	8.5	1,763	4.8	2,646	5.5
Missing	1,349	52.0	2,564	29.6	18,483	50.6	22,396	46.9
Education								
Elementary school	865	33.3	2,218	25.6	14,229	38.9	17,312	36.2
Secondary school	953	36.7	3,955	45.7	11,969	32.8	16,877	35.3
University	404	15.6	2,112	24.4	4,189	11.5	6,705	14.0
Missing	373	14.4	364	4.2	6,145	16.8	6,882	14.4
Age at birth of first child								
No children	585	22.5	2,267	26.2	7,053	19.3	9,905	20.7
<30 years	687	26.5	3,370	39.0	7,448	20.4	11,505	24.1
≥30 years	155	6.0	864	10.0	1,805	4.9	2,824	5.9
Missing	1,168	45.0	2,148	24.8	20,226	55.4	23,542	49.3
Oestrogen use								
Yes	375	14.5	1,222	14.1	5,093	13.9	6,690	14.0
No	2,220	85.5	7,427	85.9	31,439	86.1	41,086	86.0
Metformin use								
Yes	1,278	49.2	1,237	14.3	14,214	38.9	16,729	35.0
No	1,317	50.8	7,412	85.7	22,318	61.1	31,047	65.0

[a] Defined as a person who reported not smoking in 2003, 2004 and 2005

[b] Defined as a person who reported smoking in 2003 or 2004, but reported not smoking in 2005

[c] Defined as a person who reported smoking in 2005

Table 5 Incidence rate ratio for breast cancer among women using insulin glargine alone 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[a] (95% CI)	
	Insulin glargine alone	Insulin glargine in combination with other types of insulin
Unadjusted	1.91 (1.25–2.89)	0.92 (0.66–1.29)
Adjusted for		
Age	1.99 (1.31–3.03)	1.10 (0.77–1.56)
Age and metformin	1.98 (1.30–3.01)	1.11 (0.78–1.59)
Age and oestrogen	1.99 (1.31–3.02)	1.08 (0.76–1.54)
Age and BMI	1.97 (1.31–3.00)	1.16 (0.81–1.65)
Age and smoking	1.97 (1.31–3.00)	1.16 (0.81–1.65)
Age and age at onset of diabetes	1.96 (1.29–2.97)	1.16 (0.81–1.65)
Age and cardiovascular disease	2.00 (1.31–3.04)	1.10 (0.77–1.56)
Age and age at birth of first child	2.00 (1.31–3.04)	1.11 (0.77–1.56)
Multiple variables[b]	1.97 (1.29–3.00)	1.15 (0.80–1.65)
Restricted to age 35–79 years and adjusted for		
Multiple variables[b]	1.98 (1.25–3.13)	1.14 (0.78–1.67)
Multiple variables[b] and educational level	1.98 (1.25–3.13)	1.14 (0.78–1.67)

[a] Incidence rate ratio is referred to as the RR in the text

[b] Age, age at birth of first child, age at onset of diabetes, BMI, cardiovascular disease, oestrogen use and smoking

2.14 (95% 1.24–3.71) for women with three or more prescriptions dispensed for insulin glargine and 1.53 (0.49–4.79) for women with one to two prescriptions dispensed, compared with those with no prescriptions dispensed for insulin glargine. We saw no statistically significant increase in incidence rate with increasing number of daily defined doses of insulin glargine (data not shown).

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

When we studied acute myocardial infarction as an outcome and adjusted for age, age at onset of diabetes, BMI and smoking, we obtained an RR of 0.77 (0.59–1.00) for female users of insulin glargine alone, and 0.88 (0.74–1.05) for female users of insulin glargine together with other types of insulin, compared with female users of types of insulin other than insulin glargine. When investigating mortality, we adjusted for age, age at onset of diabetes, BMI, smoking and having had cardiovascular disease. Female users of insulin glargine alone 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 alone 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 alone, 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 to confound the

association than risk factors explaining only a small percentage.

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

To prevent the development of cancer having any influence on selection for observation of cancer occurrence ('reversed causality'), we performed a fixed-cohort analysis, classifying individuals according to drug prescriptions dispensed in 2005. Some individuals registered as having a drug prescription dispensed for other types of insulin may certainly have used insulin glargine before 2005 or during the observation period during 2006 and 2007. This error often causes a non-differential misclassification of exposure, which shifts the RR towards 1.0 [28]. In other words, the uncertainty surrounding the extent to which a registered prescription dispensed for insulin glargine reflects real-life use of insulin glargine limits our ability to detect the true effect on the occurrence of malignancies. This limitation does not, however, as a rule, produce a spurious result indicating an effect. Thus, if we had been able to eliminate this inaccuracy, allowing us to only study the true users of insulin glargine with respect to the development of malignancies over the relevant time period, we would probably have obtained an age-adjusted RR higher than the 1.99 we obtained for breast cancer for users of insulin glargine alone. The available information indicates that loss to follow-up was small and did not differ between the different treatment groups. We did not find any indication of reversed causality, that is, of the presence of cancer having influenced the likelihood of using, or not using, insulin glargine. The mortality rate and the incidence rate of acute myocardial infarction were lower for users of insulin glargine alone than for users of types of insulin other than insulin glargine; we have no indication that users of insulin glargine alone had a higher rate of morbidity than the comparison group.

Duration from the start of exposure of industrial agents to an excess risk of cancer is usually 10–25 years. Among users of the drug chlornaphazine, an agent used to treat polycytemia verae, an increased risk of bladder cancer was observed as early as 3–5 years after treatment initiation [29, 30]. Chlornaphazine resembles the extremely strong and remarkably species-unspecific bladder cancer carcinogen β-naphthylamine. We are not aware of any documentation of an increased incidence of cancer the year after initiation of treatment with a specific drug. Insulin glargine appeared on the Swedish market in 2003, and we do not know the percentage of users of insulin glargine who started using the drug in that year. Nevertheless, the short duration from the start of insulin glargine use to the increased incidence rate for breast cancer suggests that our results could be due to random fluctuation.

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

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

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

References

1. Mayer D, Shukla A, Enzmann H (2008) Proliferative effects of insulin analogues on mammary epithelial cells. Arch Physiol Biochem 114:38–44
2. Weinstein D, Simon M, Yehezkel E, Laron Z, Werner H (2009) Insulin analogues display IGF-I-like mitogenic and anti-apoptotic activities in cultured cancer cells. Diabetes Metab Res Rev 25: 41–49
3. Rosén M (2002) National Health Data Registers: a Nordic heritage to public health. Scand J Public Health 30:81–85
4. Hemkens LG, Grouven U, Bender R et al (2009) Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. Diabetologia. doi:10.1007/s00125-009-1418-4

5. Steineck G, Hunt H, Adolfsson J (2006) A hierarchical step-model for causation of bias-evaluating cancer treatment with epidemiological methods. Acta Oncol 45:421–429

6. Socialstyrelsen (The National Board of Health and Welfare, Sweden) (2008) Patientregistret. Available from www.socialstyrelsen.se/Statistik/statistik_amne/sluten_vard/Patientregistret.htm, accessed 18 June 2009

7. Ericson A, Eriksson M, Källén B, Westerholm P, Zetterström R (1984) Delivery outcome of women working in laboratories during pregnancy. Arch Environ Health 39:5–10

8. Statistics Sweden (2004) The Swedish Register of Education. Available from www.scb.se/statistik/UF/UF0506/Produktbeskrivning_short_English_UF0506_20040101r.doc, accessed 18 June 2009

9. Socialstyrelsen (The National Board of Health and Welfare, Sweden) (2003) Causes of Death Register. Available from www.socialstyrelsen.se/en/Statistics/statsbysubject/The_Cause_of_Death_Register.htm, accessed 18 June 2009

10. Wettermark B, Hammar N, Fored CM et al (2007) The new Swedish Prescribed Drug Register—opportunities for pharmaco-epidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf 16:726–735

11. Socialstyrelsen (The National Board of Health and Welfare, Sweden) (2008) Cancer Incidence in Sweden 2007. Available from www.socialstyrelsen.se/Publicerat/2008/10204/2008-125-16.htm, accessed 18 June 2009

12. Mattsson B, Wallgren A (1984) Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. Acta Radiol Oncol 23:305–313

13. Barlow L, Westergren K, Holmberg L, Talbäck M (2009) The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol 48:27–33

14. Gudbjörnsdòttir S, Cederholm J, Nilsson PM, Eliasson B (2003) The National Diabetes Register in Sweden: an implementation of the St. Vincent declaration for quality improvement in diabetes care. Diabetes Care 26:1270–1276

15. Trichopoulos D, Hsieh CC, MacMahon B et al (1983) Age at any birth and breast cancer risk. Int J Cancer 31:701–704

16. Rapp K, Schroeder J, Klenk J et al (2005) Obesity and incidence of cancer: a large cohort study of over 145,000 adults in Austria. Br J Cancer 93:1062–1067

17. Campbell RT, Li X, Dolecek TA, Barrett RE, Weaver KE, Warnecke RB (2009) Economic, racial and ethnic disparities in breast cancer in the US: towards a more comprehensive model. Health Place 15:855–864

18. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD (2005) Metformin and reduced risk of cancer in diabetic patients. BMJ 330:1304–1305

19. Collaborative Group on Hormonal Factors in Breast Cancer (1997) Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 350:1047–1059

20. Ellison RC, Zhang Y, McLennan CE, Rothman KJ (2001) Exploring the relation of alcohol consumption to risk of breast cancer. Am J Epidemiol 154:740–747

21. Levi F, Pasche C, Lucchini F, La Vecchia C (1996) Alcohol and breast cancer in the Swiss Canton of Vaud. Eur J Cancer 32A:2108–2113

22. Adami H-O, Hunter D, Trichopoulos D (2002) Textbook of cancer epidemiology. Oxford University Press, Oxford

23. Easton DF, Narod SA, Ford D, Steel M (1994) The genetic epidemiology of BRCA1. Breast cancer linkage consortium. Lancet 344:761

24. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE (1994) Risks of cancer in BRCA1-mutation carriers. Breast cancer linkage consortium. Lancet 343:692–695

25. Miki Y, Swensen J, Shattuck-Eidens D et al (1994) A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 266:66–71

26. Wooster R, Bignell G, Lancaster J et al (1995) Identification of the breast cancer susceptibility gene BRCA2. Nature 378:789–792

27. Ford D, Easton DF, Stratton M et al (1998) Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The breast cancer linkage consortium. Am J Hum Genet 62:676–689

28. Rothman KJ, Greenland S (1998) Modern epidemiology. Lippincott Williams & Wilkins, Philadelphia

29. Cohen SM, Shirai T, Steineck G (2000) Epidemiology and etiology of premalignant and malignant urothelial changes. Scand J Urol Nephrol Suppl (205):105–115

30. Thiede T, Christensen BC (1969) Bladder tumours induced by chlornaphazine. A five-year follow-up study of chlornaphazine-treated patients with polycythaemia. Acta Med Scand 185:133–137

31. Giovannucci E, Pollak MN, Platz EA et al (2000) A prospective study of plasma insulin-like growth factor-1 and binding protein-3 and risk of colorectal neoplasia in women. Cancer Epidemiol Biomarkers Prev 9:345–349

32. Kaaks R, Lukanova A (2001) Energy balance and cancer: the role of insulin and insulin-like growth factor-I. Proc Nutr Soc 60:91–106

33. Nam RK, Trachtenberg J, Jewett MA et al (2005) Serum insulin-like growth factor-I levels and prostatic intraepithelial neoplasia: a clue to the relationship between IGF-I physiology and prostate cancer risk. Cancer Epidemiol Biomarkers Prev 14:1270–1273