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COMMENTARY

Diabetes therapy and cancer risk: causal effects and other plausible explanations

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Abstract Four reports in *Diabetologia* presented data on the association between hypoglycaemic agents and the risk of cancer. One study showed a higher risk of cancer overall in subjects with diabetes receiving insulin or sulfonylureas than in those on metformin. In another study, the risk of cancer overall increased with dose for any type of insulin and, among high doses, insulin glargine (A21Gly,B31Arg, B32Arg human insulin)-only users had a higher risk than subjects on human insulin. In two studies, users of insulin glargine alone had a higher risk of breast cancer than those on other insulins, a third study found no association. Whether these associations are causal or at least partially explained by chance or biases such as confounding, reverse causation, selection or detection biases is arguable. Current epidemiological evidence is insufficient to confirm a carcinogenic effect of specific insulins on specific cancers. However, the potential dose effect of insulin overall, and insulin glargine in particular, on colon and breast cancer deserves further attention.

Keywords Cancer · Insulin analogues · Insulin therapy · Metformin · Type 2 diabetes

Abbreviation
OHA Oral hypoglycaemic agent

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Introduction

Whilst both diabetes type 1 [1] and type 2 [2] have been positively associated with a growing number of human cancer sites and types, data on the effect of diabetic treatments on the risk of cancer are scarce and inconsistent. Previous studies reported a higher risk of colon cancer in insulin users [3, 4] and a lower risk of cancer and cancer mortality in metformin users [5, 6]. Four reports in *Diabetologia* presented new data on the association between oral hypoglycaemic agents (OHAs) and the risk of cancer [7–10]. Although these studies differ in methodological aspects, they are all trapped between three perfect epidemiological storms: confounding by indication; assessment of aetiologically relevant timing of exposure; and intensity of diagnosis. First, there is usually a reason for a patient to initiate, maintain or change a given treatment; such reasons might be associated with the risk of cancer diagnosis. Second, given the latency period for most cancers we would, a priori, expect long-term effects after an induction period of many years and, more often, several decades. Third, if the stage of disease or a particular treatment regimen is related to the frequency of clinical contact, this could reduce the time between onset and diagnosis of cancer, resulting in different cancer-detection rates for different treatments. We analyse below the four papers with these challenges in mind.

UK study by Currie et al.

Using electronic medical record data from a UK general practice network, Currie et al. studied the risk of specific cancers in a cohort of 62,809 individuals >40 years of age with primary type 2 diabetes who started treatment with OHAs or insulin between 2001 and 2006 [7]. After an

average of 2 years of follow-up, the incidence of cancer (per 100 person-years) was 0.9 for metformin monotherapy, 1.6 for sulfonylurea monotherapy, 1.1 for metformin plus sulfonylurea and 1.3 for insulin initiators. Metformin users were youngest, had a shorter duration of diabetes and lower HbA_{1c} levels, had visited their doctors less frequently and were less likely to smoke or to have prior solid tumours. To correct for this lack of comparability among treatment groups, the authors included selected covariates in the Cox proportional hazards models. Compared with metformin monotherapy, the adjusted hazard ratios were 1.1 (95% CI 1.0–1.2) for metformin plus sulfonylurea, 1.4 (95% CI 1.2–1.5) for sulfonylurea monotherapy, 1.4 (95% CI 1.3–1.6) for insulin and 1.1 (95% CI 1.0–1.3) for non-pharmacological treatment. The risk for insulin regimens was specifically elevated for colorectal cancers (HR 1.7) and pancreatic cancers (HR 4.6), but not for breast or prostate cancers. Among insulin initiators, users of insulin glargine (A21Gly,B31Arg,B32Arg human insulin), long-acting human insulin, biphasic analogue and human biphasic insulin had similar cancer rates. Although based on small numbers, the previously suggested positive association between insulin glargine and breast cancer was not confirmed; the HR of breast cancer for insulin glargine users vs other insulin users was 0.86 (95% CI 0.42–1.8). Prescription of metformin among insulin users was associated with HR 0.54 (95% CI 0.43–0.66).

The authors present informative survival curves (note different scales), which show a divergence in the overall incidence of cancer among treatments during the first year; but almost parallel trajectories afterwards. It is not clear in the manuscript whether the confounder-adjusted curves allowed for time-varying HRs. The curves are surprising for both biological and methods-related reasons. First, known carcinogens have longer latency periods. The authors were aware and excluded 'patients with less than 6 months of exposure in order to ensure sufficient degree of exposure to potentially influence development of a solid tumour'. The immediate divergence in risks argues against a causal effect and in favour of reverse causation, which would imply that a preclinical cancer might have triggered intensification of therapy. Such bias is biologically plausible, particularly for pancreatic cancer, and is consistent with the dramatic differences observed for this tumour already within months of treatment initiation. Although the outcome was defined as 'progression of tumours', such rapid progression of existing tumours, attributable to one external cause, is largely unknown in cancer epidemiology. Second, cancer was ascertained the first time a code for a solid tumour was entered in the electronic medical record database, and the diagnoses were not validated. This method is usually unable to distinguish between initiation, progression or just clinical detection of cancer. The date of first symptoms for colon and other types of cancer might have occurred months before the date of diagnosis, further supporting the reverse-causation theory. Third, by design, there cannot be tumour diagnoses during the first 6 months if follow-up started on 'the date of observed treatment initiation or switching', cohort membership was terminated with the 'record of the primary or secondary outcomes' and individuals had to survive free of cancer for 6 months on a given regimen in order to be eligible.

As the authors recognise, many individuals receiving the OHA are true initiators of pharmacological treatment, while the combined sulfonylurea and metformin cohort and the insulin cohorts include mainly switchers from other therapies. Thus, insulin initiators had a longer duration of diabetes and had been exposed to OHAs, survived without cancer, but no longer responded to OHAs. An impaired glycaemic control might share common causes with cancer, be it the consequence of tumour growth or of more clinical visits and hence increased opportunities for diagnosis. In addition, although the outcome is defined as 'first record of any solid tumour cancer', 4.3% of metformin users and 6.4% of insulin users had previous solid tumours at baseline, which affects both the risk of future cancer and the intensity of diagnosis. It is difficult to control for all these differences in the analysis; better information (e.g. on smoking history or healthcare utilisation) or modelling of measured covariates (e.g. age or duration of diabetes), and adjustment for unmeasured confounders could have moved the HR estimates further towards the null. Just excluding individuals with prior cancer recorded in the database moved the estimate from 1.42 to 1.35 for insulin-based regimens vs metformin. Regarding the comparisons with untreated diabetes, they are difficult to interpret because this group is very different clinically, includes follow-up based on the presence of future prescriptions of diabetes-related medications (i.e. person-time without cancer by definition) and had longer run-in periods than other exposed groups (3 years vs 6 months).

The authors conclude that there is a protective effect of metformin. Based on the findings, an alternative causal interpretation would be that sulfonylurea and insulin-based regimens increase the risk of colon and pancreatic cancer in individuals with diabetes. Since the study could not examine dose effects, the apparent protective effect of metformin among insulin users might be due to lower doses of insulin among those individuals on concomitant metformin. Distinguishing between these two scenarios is of great scientific interest but limited clinical relevance for the management of diabetes, where we need to consider the comparative safety (and effectiveness) of the available therapeutic options. It would be relevant, however, if we were to propose metformin as chemopreventive agent for pancreatic cancer, which would be speculative at this point. Most importantly, as discussed above, we first need to contemplate non-causal interpretations for the association,

such as reverse causation and confounding. In addition, if we understood correctly, concomitant metformin use was defined as 'at any time during insulin exposure', independently from follow-up time. Therefore, the opportunity for exposure was lower in individuals who developed cancer, who had fewer months of follow-up to receive metformin, thus potentially inducing a spurious inverse association between the drug and the outcome. In summary, as the authors wrote, 'it would be premature to assume causal relationships'.

German study by Hemkens et al.

Using computerised claims data from a German health insurance plan, Hemkens et al. studied the risk of any cancer and all-cause mortality in a cohort of 127,031 individuals >18 years of age who started treatment with either human insulin or an insulin analogue between 2001 and 2005 [8]. Individuals who received more than one insulin concomitantly, switched or added insulins during follow-up or discontinued treatment were excluded. After an average of 1.6 years of follow-up the incidence of cancer per 100 person-years was 2.5 in individuals using human insulin, 2.2 in those using insulin aspart (B28Asp human insulin), 2.1 in those using insulin lispro (B28Lys,B29Pro human insulin) and 2.1 in those using insulin glargine. However, treatments groups were not directly comparable; individuals had different distributions of age, sex, history of hospital stay, concomitant medications, including OHAs, and geographic region.

Compared with human insulin, the adjusted HR estimates remained close to 1.0 for insulin aspart and insulin lispro. However, the HR for insulin glargine changed from 0.86 to 1.14 upon 'adjustment for dose', and moved to 1.18 with further adjustment for selected covariates. The risk of cancer increased with higher average doses of human insulin: the incidence values per 100 person-years were 1.7, 2.4 and 3.1 for <20, 20–40 and >40 U, respectively. The corresponding incidence values for insulin glargine were 1.9, 2.0 and 5.3. In comparison, the adjusted HR for insulin glargine vs human insulin was 1.6 within doses >40 U, but around 1 for lower dose strata. However, the mean insulin dose was substantially lower for insulin glargine (i.e. patients using insulin glargine needed lower doses, thus either the individuals, the drug effects or both are different) and the 95th percentile was 59 U for insulin glargine and 100 U for human insulin (i.e. within the >40 U category doses are higher for human insulin than for insulin glargine). Therefore, dose stratification does not guarantee the comparability of the treatment groups; residual bias could result in under- or overestimation of the HR. Regarding all-cause mortality, the three insulin analogues were associated with slightly lower death rates than human insulin, although the adjusted dose-specific HR estimates for insulin glargine ranged from 0.76 for 10 U to 1.2 for 50 U.

This study was limited by the lack of information on potentially relevant confounders (e.g. diabetes type, number of years with the diagnosis, smoking, body mass index), specific cancers and specific causes of death. Smoking, weight and diabetes duration might not be important sources of confounding within insulin users despite their association with cancer risk because, based on data from Currie et al. [7] these characteristics are homogeneous among insulin initiators. Yet, the German study combined individuals with diabetes type 1 and 2 and could not adjust for it. Based on data from the SDRN Epidemiology Group (see below) [9], adjustment for type of diabetes could have reduced the HR by up to 40%. Therefore, residual confounding by measured or unmeasured characteristics cannot be ruled out as an explanation for an HR of only 1.18. If higher insulin glargine doses were associated with type of diabetes, body mass index or other risk factors for cancer, confounding could also explain the apparent dose effect. Moreover, the exchangeability of the treatment groups could have been compromised if switching or adding insulins, which resulted in exclusion from the study, was associated with the risk of cancer, e.g. if the growing tumour affects glycaemic control.

In addition, as in the UK study [7], the increased risk for insulin glargine is observed within 1 to 2 years of treatment initiation. This finding is compatible with an effect on tumour progression, but also with detection bias. Two pieces of evidence support the latter theory. First, the HR for high doses of insulin glargine decreased when skin cancer, precancerous lesions and in situ carcinoma—which are particularly sensitive to increased diagnostic intensity—were excluded. Second, the more frequent hospitalisations in the human insulin group during the 3 years before the start date could have resulted in higher detection rates for preclinical cancers. These patients with diagnosed cancer were excluded, while the corresponding undiagnosed cancers would have been detected in the insulin analogue groups during the study period. In fact, the proportion of individuals excluded due to diagnosis or suspicion of a malignant neoplasm within 3 years prior to first prescription was 14.8% for the human insulin cohort and 11.6% for the insulin glargine cohort. On the other hand, a projection of these frequencies of health service utilisation and cancer-detection rates would have predicted a higher risk of cancer among users of human insulin, therefore suggesting that the results might actually underestimate the effect of insulin glargine, as suggested by the authors.

Although analysing total cancer incidence might provide a useful guide for clinical management, this approach is inadequate for causal inference; similar to non-malignant diseases, each cancer site and type has its unique web of causes. The disconcerting association with all cancers is

compatible with a larger effect on the risk of few specific cancers, but also with a systematic bias. Similarly, even a 30% increase in the risk of cancer for high doses of insulin glargine compared with human insulin can hardly explain the reported 20% increase in all-cause mortality. The authors plan to conduct further analyses of specific tumours and death causes, which will be helpful.

Swedish study by Jonasson et al.

Through linkage of Swedish national registers, Jonasson et al. identified a cohort of 114,841 individuals aged 35–84 years and without prior cancer history who were dispensed insulin between 1 July and 31 December 2005 and ascertained the incidence of cancer from 1 January 2006 to 31 December 2007 [10]. There were no differences among the groups taking insulin treatments for cancer overall, nor any statistically significant increased risk with increasing daily defined doses of insulin glargine. For breast cancer, compared with users of insulin monotherapy other than insulin glargine, the HR was 2.0 (95% CI 1.3–3.0) for users of insulin glargine only and 1.2 (95% CI 0.8–1.7) for users of insulin glargine in combination with other insulins. Parallel analyses resulted in HRs of 0.8 (95% CI 0.6–1.0) for myocardial infarction and 0.8 (95% CI 0.7–1.0) for mortality for female users of insulin glargine monotherapy. Neither gastrointestinal nor prostate cancers were associated with type of insulin.

The baseline characteristics differed among treatment groups, but the HRs for glargine vs non-glargine insulins changed little after adjustment, suggesting a limited role of confounding. To maintain the comparability of the exposure groups and avoid reverse causation, the authors simulated an intention-to-treat analysis by defining exposure based on prescriptions in July to December 2005 without regard to potential treatment changes during follow-up. While avoiding the potential biases introduced with the 'as-treated' analysis, the intention-to-treat analysis typically introduces an exposure misclassification that biases any association towards the null, which is dangerous when studying safety. This analysis can also, as the authors suggest, bias the estimates away from unity. In any case, they could have presented compliance curves. Also, as follow-up started in 2006 and they assessed prevalent use, there was an implicit latency period of up to 6 months until the beginning of follow-up plus the time subjects could have been using insulin before July 2005. In the presence of an immediate effect on cancer progression, the design would underestimate it. The authors challenged their own finding with multiple sensitivity analyses; the twofold increased risk of breast cancer for insulin glargine only vs non-glargine insulin only did not go away. Yet they conclude that the association with breast cancer could be attributable to random fluctuation.

Scottish study by the SDRN Epidemiology Group

The SDRN Epidemiology Group linked the Scottish diabetes clinical database with cancer and death registries to study the risk of cancer on a cohort of 36,254 individuals receiving treatment with either insulin glargine or other types of insulin during a fixed 4 month period in 2003 (fixed cohort), and on a cohort of 12,852 individuals with type 2 diabetes who started treatment between 2002 and 2005 (incident cohort) [9]. The accuracy of cancer ascertainment and date of diagnosis has been monitored and validated in the registry. They used three different analytical approaches and adjusted for confounders step by step to explore potential sources of bias.

In their fixed cohort, there were 32,295 individuals using non-glargine insulin and 447 using insulin glargine only. Compared with non-glargine insulin users, the adjusted HR for cancer overall was 1.7 (95% CI 1.0–3.0) for individuals using insulin glargine only and 0.9 (95% CI 0.6–1.4) for those using both glargine and non-glargine insulins during the fixed period. The HR for breast cancer was 3.7 (95% CI 1.1–12.7) for individuals using insulin glargine only. Insulin-glargine-only users were older, had started insulin more recently, had more often type 2 diabetes, had worse glycaemic control, used OHAs more frequently and had a recent history of cancer more often than users of other insulin monotherapies. Confounding was substantial; the HR estimate for total cancers changed from 2.6 to 1.7 after adjusting for potential confounders, suggesting that residual confounding might explain part of the remaining association. Similarly, the negative association found for insulin glargine when used in combination with other insulins changed from 0.39 to 0.88. Moreover, in the fixed-cohort approach, prevalent users could have been using insulin for a long time, particularly users of insulins other than insulin glargine. Therefore, cancers diagnosed after treatment initiation but before inclusion in the cohort would be excluded. In the presence of any association, causal or not, between insulin initiation and cancer progression, the design would have missed cases, particularly among users of insulins other than insulin glargine, therefore inducing a higher relative risk for insulin glargine. This concern is supported by the data. Not surprisingly, the proportion of new users was lowest among individuals using non-glargine insulin and, interestingly, the cancer rate was 1 per 100 person-years among prevalent users and 1.7 among new users of non-glargine insulin. The authors were aware of this potential source of bias and therefore conducted analyses restricted to new users of any insulin treatment: the incident cohort design.

In their incident cohort, there were 10,262 individuals using non-glargine insulin and 1,900 using insulin glargine only. Compared with new users of non-glargine insulin, the adjusted HR for cancer overall was 0.9 (95% CI 0.6–1.2) for new users of insulin glargine only and 1.2 (95% CI 0.7–2.1) for those using a combination of insulin glargine and non-glargine insulin; the HR for breast cancer was 1.5 (95% CI 0.6–3.6) for insulin glargine only. The impact of confounding adjustment was modest. Regarding latency time, as the authors considered entry time in the cohort as the end of the 4 month period required to classify exposure, only acute effects within months of initiation would have been underestimated.

Both the fixed- and the incidence-cohort designs were analysed with an 'intention-to-treat' approach to avoid biases that would occur if preclinical cancer was somehow associated with changes in treatments (i.e. reverse causation). As warned by the authors, this approach can bias towards the null, although it can also bias away from the null under certain conditions. Therefore the SDRN Epidemiology Group conducted a third group of analyses classifying individuals 'as treated' over the study period. Compared with users of non-glargine insulin only, the adjusted HR for cancer overall was 1.5 (95% CI 1.1–2.0) for users of insulin glargine only and 0.7 (95% CI 0.5–0.8) for those using insulin glargine and non-glargine insulin; the HR for breast cancer was 2.0 (95% CI 0.9–4.5) for insulin glargine only. These analyses share with the fixed-cohort design the potential biases due to confounding and to depletion of susceptible individuals among prevalent users discussed before. In addition, the 'as-treated' analysis is prone to reverse causation, as stated by the authors. All these biases probably compensated for the actualisation of exposure over time as the HRs from the 'as-treated' analysis were closer to null than those from the intention-to-treat analysis in the fixed cohort (in theory, more misclassified).

The three analytical approaches consistently showed a lack of association for insulin glargine in combination with other insulins. This finding argues against a causal effect, unless polytherapy was associated with lower insulin glargine doses or concomitant human insulin modified the effect of insulin glargine, for example, competing for binding sites in receptors. A higher risk was found for insulin glargine in monotherapy, but only when prevalent users were considered. This finding would be compatible with bias induced by depletion of susceptible individuals from the longer-term users of non-glargine insulin if treatment initiation was somehow associated with a higher cancer risk; as well as with a duration or cumulative dose effect for insulin glargine (i.e. prevalence is a function of initiation and duration of treatment). It would have been informative to see adjusted survival curves after treatment initiation for different insulins.

The authors concluded that these findings refute the theory of an association between insulin glargine therapy and total cancer and that the data are reassuring. For breast cancer, the three analyses resulted in HRs above 1 for users of insulin glargine only vs users of non-glargine insulin, with confidence intervals from the three estimates overlapping. The authors concluded that there was no increase in breast cancer rate associated with insulin glargine use, and that the associations were more likely the result of allocation of less healthy individuals to the simple-to-use insulin glargine regimen than to causal effects.

Discussion

In summary, one study [7] showed a higher risk of cancer overall in individuals with diabetes receiving insulin or sulfonylureas than in those using metformin; the risk was similar for different insulin formulations at the doses used in clinical practice. In another study [8], the risk of cancer overall increased with dose for any type of insulin and, among doses >40 U, users of insulin glargine only had a higher risk than individuals using human insulin. In two studies [9, 10], users of insulin glargine alone had a higher risk of breast cancer than those using other insulins, another found no association [7] (pooled HR 1.6; 95% CI 1.1–2.2). Whether these associations are causal or at least partially explained by chance or biases such as confounding, reverse causation or detection bias is arguable.

In the absence of randomisation, researchers seek homogeneity among treatment groups by restricting the analysis to patients with diabetes and comparing different treatments within the group. Further, they used regression models to adjust for potential confounders and account for competing risks. Yet hyperinsulinaemia or other genetic or environmental factor associated with diabetes progression may play a carcinogenic role and remains as a potential source of bias. It is worth noting that insulin glargine has been recommended for individuals not responding to glucose-lowering agents alone who need a combination of OHA and insulin, individuals with hypoglycaemia problems and those who need help with insulin administration. Thus, individuals who receive only insulin glargine at high doses and/or in monotherapy may be a high-risk group for cancer due to factors difficult to measure and control in observational studies.

The short periods of follow-up needed to observe an association in some studies argue against a causal effect on the initiation of cancer. Although immediate effects would be compatible with accelerations in the progression of existing cancers, resulting in clinical manifestations and diagnosis soon after initiation of therapy, such rapid promotion is unlikely based on existing biological knowledge and clinical experience. Rather, the temporal relationship may be reversed, i.e. individuals with undiagnosed cancer may have worse glycaemic control and receive higher insulin doses. Such a mechanism is, however,

unlikely in, for example, cancers of the breast and prostate because the tumour burden is usually minimal at the time of diagnosis. Alternatively, initiation or intensification of therapy may result in more clinical visits and increased opportunity for diagnosis.

Sanofi-aventis, the manufacturer of insulin glargine, analysed data from 31 randomised clinical trials comparing insulin glargine with NPH insulin and other comparators [11]. Individuals were therefore comparable within individual studies. However, the individual studies were too small to be informative and the authors pooled the data. In patients with type 1 diabetes the incidence of malignancies was 0.4% in the insulin glargine group and 0.1% in the other basal insulin group (RR 4, based on small numbers). In patients with type 2 diabetes the association changed with duration: (1) in five studies of 28 weeks' duration, the incidence of malignancies was 0.78% in the insulin glargine group and 0.46% in the NPH insulin group (RR 1.7; no breast cancer cases); (2) in one study of 52 weeks' duration, the incidence of malignancies was 1.0% in the insulin glargine group and 2.5% in the NPH insulin group (RR 0.4); and (3) in one study of 5 years' duration, the incidence of malignancies was 3.9% in the insulin glargine group and 6.2% in the NPH insulin group (RR 0.6). In trials comparing insulin glargine with either oral agents or insulin other than NPH insulin the incidence of malignancies was 0.58% (six cases) in the insulin glargine group and 0% in the comparison groups. In the pooled analysis, insulin glargine did not increase the risk of cancer, including breast and colon cancer. However, as in observational studies, results from these randomised studies are compatible with a short-term imbalance of malignancies in individuals treated with insulin glargine. These results underscore the importance of presenting survival curves over time in order to understand the apparent paradoxical short-term association.

Novo Nordisk, the manufacturer of insulin detemir (B29Lys(ε-tetradecanoyl),desB30 human insulin), pooled data from their randomised studies as well [12]. The overall rate of malignant neoplasms per 100 person-years was 0.87 for insulin detemir and 1.27 for insulin glargine; the corresponding rates for breast cancer were 0.11 (n=1) and 0.48 (n=3), respectively. The studies were too short and too small to allow any conclusion regarding insulin glargine.

If large randomised trials on the effect of specific diabetes treatments on cancer are not feasible, future observational studies should consider the lessons learnt from the four epidemiological papers in *Diabetologia* (see textbox 'some suggestions for future research'). Cancer risk would have to be considered in the context of the overall comparative safety and efficacy of each therapy.

Some suggestions for future research

- Consider specific predefined cancers and specific cancer deaths
- Restrict the outcome to primary cancer diagnosis and exclude individuals with prior cancer history
- Validate the outcomes and dates of first symptoms
- Consider latency times that accommodate what we know about cancer biology, namely that years are usually required before we observe causal effects in cancer aetiology
- Evaluate a potential short-term triggering of diagnosis
- Predefine comparison groups (e.g. insulin glargine monotherapy vs human insulin)
- Include only new users (i.e. initiators) of a given drug
- Use intention-to-treat approaches (i.e. do not censor a participant when a treatment is stopped or changed) but also present adherence curves over follow-up
- Describe the prescription patterns for insulin glargine and other insulins in clinical practice
- Adjust adequately for all baseline factors associated with the prescription of specific treatments and with the risk of specific cancers
- Present crude and adherence-adjusted survival curves allowing for time-varying HRs
- Explore dose effects
- Explore the potential confounding or intermediary effect of circulating levels of insulin
- Conduct sensitivity analyses to evaluate the magnitude and direction of potential residual biases

In conclusion, current epidemiological evidence is insufficient to confirm or refute a carcinogenic effect of specific insulins on specific cancers. We agree with the criticisms by Pocock and Smeeth [13] regarding the study limitations. However, we believe there are still reasons for concern. The potential dose effect of insulin overall, and insulin glargine in particular, on colon and breast cancer deserves further attention. Although not specifically assessed in the four studies published in *Diabetologia*, studying the effects of insulins on hepatocellular cancer would be particularly interesting given the strong association previously reported between diabetes and this cancer [14].

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