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Diabetes, insulin treatment, and cancer risk: what is the evidence?

Madona Azar and Timothy J Lyons*

Address: Harold Hamm Oklahoma Diabetes Center, University of Oklahoma Health Sciences Center, Section of Endocrinology, Diabetes & Metabolism, 1000 North Lincoln Suite 2900, Oklahoma City, OK 73104, USA

* Corresponding author: Timothy Lyons (timothy-lyons@ouhsc.edu)

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Abstract

Diabetes, in particular type 2, is associated with an increased incidence of cancer. Although the mortality attributable to cancer in type 2 diabetes is overshadowed by that due to cardiovascular disease, emerging data from epidemiologic studies suggest that insulin therapy may confer added risk for cancer, perhaps mediated by signaling through the IGF-1 (insulin-like growth factor-1) receptor. Co-administered metformin seems to mitigate the risk associated with insulin. A recent series of publications in *Diabetologia* addresses the possibility that glargine, the most widely used long-acting insulin analogue, may confer a greater risk than other insulin preparations, particularly for breast cancer. This has led to a heated controversy. Despite this, there is a consensus that the currently available data are not conclusive and should not be the basis for any change in practice. Further studies and more thorough surveillance of cancer in diabetes are needed to address this important issue.

Introduction and context

The associations between diabetes and cancer have been the subject of debate for over a century. The length of this debate suggests, perhaps, that any such associations are relatively weak, and it is safe to say that most practicing diabetologists do not view cancer as a specific, diabetes-associated risk in day-to-day practice. That diabetes is not more clearly associated with cancer is surprising, since diabetes may be viewed as a disease of increased intracellular oxidative stress, as well as accelerated 'biochemical aging' caused by the accumulation of 'advanced glycation end-products' (AGEs) on proteins and other macromolecules (reviewed in [1]). An additional concern is the role of insulin, which, in various forms, is increasingly used in the management of type 2 diabetes, a condition that is now epidemic worldwide. Specifically, the ability of insulin to bind and activate the insulin-like growth factor-1 (IGF-1) receptor has raised concerns that it may promote the growth of nascent malignancies and even the establishment of new ones. Such concerns are supported by animal and cell culture studies.

With this background, there has been a recent surge in interest in the role of diabetes, insulin therapy, and specifically the effects of newer forms of insulin in promoting cancer. Recent rigorous epidemiologic studies have confirmed that type 2 diabetes does indeed confer increased risk for certain types of malignancies, in particular breast [2], colon [3,4], and pancreatic [5,6] tumors. Many patients with type 2 diabetes eventually require insulin, and the long-acting insulin analogue, glargine, is one of the most commonly used agents. Several recent studies have demonstrated the potential mitogenic and anti-apoptotic effects of glargine on cultured cancer cells, and have implicated activation of the IGF-1 pathway [7,8]. However, the clinical implications remain controversial, particularly when studies pertaining to untransformed cells did not support any mitogenic potential [9]. In addition, according to some authors [10,11], glargine compared with human insulin does not seem to display increased mitogenic effects, despite its higher affinity for the IGF-1 receptor [10]; rather, any type of insulin has the potential to promote growth in cancer cells, especially if administered at

sufficiently high, supra-physiologic doses. The question now is whether glargine is associated with increased cancer risk compared with other commonly used forms of insulin. This question has come to the fore with the publication of several studies in *Diabetologia* [12-15], which will be reviewed briefly here.

Recent advances

The epidemiologic study that initiated the recent debate was performed in Germany [12] and suggested a specific cancer risk associated with glargine. Based upon the mixed opinions of six reviewers, the editors of *Diabetologia*, the journal to which it was submitted, commissioned three additional studies [13-15], aiming to confirm or refute its findings.

In the initial study, Hemkens *et al.* [12] followed 127,031 German patients who were being treated with human insulin and human insulin analogues (aspart, lispro, or glargine) over a mean of 1.6 years between January 1998 and June 2005. Those on two insulin analogues or a combination of human insulin and an analogue were excluded from the analysis. Patients with known or suspected malignant disease within 3 years prior to study start were also excluded. The primary outcome was occurrence of a malignant neoplasm, and the secondary outcome was all-cause mortality. The gross malignancy incidence rates for human insulin, aspart, lispro, and glargine were 2.50, 2.16, 2.13, and 2.14 per 100 patient-years, respectively, in the unadjusted analysis. However, when the data were adjusted for daily insulin dose, glargine was found to be associated with a greater risk of malignancy, and the risk was incremental with higher glargine doses when compared with human insulin {adjusted hazard ratio [HR] of 1.09 for a daily dose of 10 IU [95% confidence interval (CI) 1.00-1.19], 1.19 for a daily dose of 30 IU [95% CI 1.10-1.30], and 1.31 for a daily dose of 50 IU [95% CI 1.20-1.42]}. Aspart and lispro were not associated with an increased risk for cancer compared with human insulin. In addition, regardless of the type of insulin, higher doses and longer duration of exposure increased the risk of malignancy. Finally, the mean insulin dose until occurrence of a neoplasm (cumulative dose divided by time until an event) was significantly lower for glargine (25.9 IU/day) than for human insulin, aspart, and lispro (43.8, 38.9, and 36.2 IU/day, respectively). The major weaknesses of the study included the fact that patients were not allocated to treatment groups in a prospective manner and that insulin dose was calculated during follow-up from mean values, and not determined at baseline. In addition, the exclusion of patients on combination insulin therapy may not reflect common practice, in which patients are typically on basal/bolus regimens requiring the use of different types of insulin. Finally, the duration of diabetes, as well as smoking status, body mass index (BMI), and other potential confounding factors were not taken into account.

The three additional, commissioned studies were published in the same issue of *Diabetologia*. In Sweden, Jonasson and colleagues [13] evaluated 114,842 patients with diabetes on insulin and noted that women on glargine alone, but not glargine combined with other types of insulin, had a higher risk of breast cancer than women on other types of insulin (HR adjusted for age, smoking, BMI, and other confounding factors was 1.97, 95% CI 1.29-3.00). However, this increased risk was not associated with an increased mortality rate; instead, all-cause mortality was actually decreased in women on glargine alone versus women on other types of insulin (relative risk [RR] 0.83, 95% CI 0.71-0.96). The associations with other malignancies such as prostate and gastrointestinal tumors did not reach statistical significance. No analysis taking into account insulin dose was possible in this study, and therefore the incremental risk conferred by higher doses as observed by Hemkens *et al.* [12] could not be supported or refuted. The short duration of exposure and observation as well as the lack of data on how much insulin the patients were taking limit the strength of the conclusions.

In a study in Scotland, no increased risk of total or site-specific cancer associated with overall glargine use was found in a cohort of 12,852 patients followed for 4 years [14]; in particular, no increase in breast cancer risk (HR 1.49, 95% CI 0.79-2.83) was found. However, exclusive use of glargine did seem to confer higher risk (adjusted HR 3.39, 95% CI 1.46-7.85), but the number of cases was small (six events). In addition, glargine-only users tended to be older, were more likely to be women, and to have a higher BMI, reflecting a baseline imbalance. In addition, the effect of concomitantly administered drugs was not taken in account. Finally, the restricted use of glargine in Scotland may have contributed to a skewing of the results, since there were a limited number of patients taking this form of insulin.

In a UK general practice setting, Currie *et al.* [15] studied 62,809 patients with diabetes on metformin, sulfonylurea monotherapy, a combination of both, or insulin therapy. The latter were further divided into glargine-treated versus other human insulin-treated (long-acting, biphasic, and biphasic analogue). The results indicated that any type of insulin therapy increased the risk of occurrence of solid tumors and that concomitant metformin therapy attenuated this effect. Indeed, the adjusted HRs relative to metformin monotherapy were

1.08 (95% CI 0.96-1.21) for the metformin/sulfonylurea combination, 1.36 (95% CI 1.19-1.54) for sulfonylurea alone, and 1.42 (95% CI 1.27-1.60) for insulin-based therapies. Concomitant metformin therapy decreased the risk of malignancy associated with insulin by 46% (HR 0.54, 95% CI 0.43-0.66). When compared with glargine, other human insulins displayed comparable rates, suggesting no added risk attributable to glargine (adjusted HR 1.24, 95% CI 0.90-1.17 for basal human insulin; HR 0.88, 95% CI 0.66-1.19 for biphasic human insulin; and HR 1.02, 95% CI 0.76-1.37 for analogue biphasic insulin). Malignancies that had the strongest association with insulin therapy compared with metformin were colorectal (HR 1.69, 95% CI 1.23-2.33) and pancreatic (HR 4.63, 95% CI 2.64-8.10) tumors. Breast and prostate cancer risks did not seem to be affected by treatment with insulin or insulin secretagogues, and a prior history of solid tumor strongly increased the overall risk (HR 3.86, 95% CI 3.46-4.31).

In a letter published in a subsequent issue of *Diabetologia*, Rosenstock *et al*. [16], reported a study of glargine versus neutral protamine Hagedorn (NPH) insulin in type 2 diabetes patients randomly assigned to one insulin or the other for over 4 years. Although malignancy risk was not a primary endpoint for the study, no increased cancer risk with glargine compared to NPH was found (RR 0.90, 95% CI 0.64-1.26).

Home and Lagarenne [17], using the sanofi-aventis 'Pharmacovigilance database' for all randomized company-sponsored clinical trials, published a systematic review of 31 trials comparing glargine to other agents (NPH for most studies). No evidence for an increased risk of malignancy attributable to glargine was found (RR 0.90, 95% CI 0.60-1.36). All but one of these studies lasted less than 12 months (on average, 6 months), so their major limitation was the short duration of exposure and follow-up. Indeed, the majority of reported cases of malignancy were derived from the study of Rosenstock and colleagues [16], discussed above, in which follow-up exceeded 4 years.

Finally, a meta-analysis comparing cancer risk associated with another new, long-acting insulin, insulin detemir, versus NPH and glargine was performed. It used data from randomized controlled trials sponsored by Novo Nordisk (Bagsvaerd, Denmark) and found comparable malignancy risks associated with detemir and glargine in the five trials that compared both drugs. However, the number of events was very small (n = 8; event rate per 100 exposure-years = 0.87 for detemir, and n = 8; event rate per 100 exposure-years = 1.27 for glargine) [18].

The debate has, not surprisingly, raised considerable controversy. The issues are highly emotive: cancer and diabetes eventually affect a large proportion of the world's population. In addition, there are enormous financial implications surrounding the controversy, and unfortunately, complex issues tend to be oversimplified and are often sensationalized. Either a diagnosis of cancer or the institution of insulin therapy for diabetes provokes great anxiety in many people. Criticism of the publication of the *Diabetologia* papers came in the correspondence section of *The Lancet*, where Pocock and Smeeth [19] raised concerns regarding the quality of the statistical analyses and contended that these analytical flaws, especially in the German paper, had raised unsubstantiated anxieties. They criticized the Swedish study for its finding of an association of insulin glargine with breast cancer [13], arguing that the latter was not a 'pre-defined site for analysis' but rather a secondary finding ultimately not 'confirmed by the Scottish study' [14] (the latter did find an increased risk of breast cancer associated with the exclusive use of glargine, but only affecting very few, older patients). Further criticism came in an editorial by Garg, Hirsch, and Skyler [20] in *Diabetes Technology and Therapeutics*, questioning the motivations behind the German study and raising concerns similar to those brought up by Pocock and Smeeth [19]. This paper also emphasized the lack of evidence of an increased overall cancer risk associated with glargine based on the Swedish, Scottish, and UK studies, concluding that 'glargine use should not be discontinued based on unsubstantiated allegations.' The letter of Pocock and Smeeth elicited a prompt response from the editor of *Diabetologia* [21]. The editor, while acknowledging the imperfections of the studies (which he had already discussed in detail in an accompanying editorial [22]), argued that the epidemiologic data cannot and should not be dismissed, especially when considered in the context of animal and cell culture work, but rather should generate further research to define risk. Indeed, in his initial editorial on the subject [22], he had earlier stated that 'the evidence presented in this set of papers is sufficient to establish that there is a case to answer, but is entirely insufficient to bring a verdict.' At least on the latter conclusion, all parties agreed.

Implications for clinical practice

These thought-provoking studies, although inconclusive, do raise concerns about the long-term effects of diabetes itself, insulin treatment, and specifically, glargine, on cancer development. It must be remembered that the greatly increased mortality among patients with diabetes has little to do with cancer, but instead is related to

vascular complications. The overall benefit-to-risk ratio of good glycemic control is likely to support extensive use of insulin. All are agreed that the current evidence does not warrant any change in clinical practice, specifically with regard to the use of glargine. Further research will need to address the relationship between diabetes, insulin, insulin analogues and secretagogues, and cancer. It will also explore potentially protective effects of metformin and perhaps the most tantalizing question: why is diabetes not more strongly associated with cancer?

Abbreviations

BMI, body mass index; CI, confidence interval; HR, hazard ratio; IGF-1, insulin-like growth factor-1; NPH, neutral protamine Hagedorn; RR, relative risk.

Competing interests

The authors declare that they have no competing interests.

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